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NEWS 4	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 5	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 6	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 7	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 8	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 9	MAR 22	EMBASE is now updated on a daily basis
NEWS 10	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 11	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 12	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 13	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 14	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS 15	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS 16	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 17	MAY 11	KOREAPAT updates resume
NEWS 18	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 19	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 20	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 21	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS EXPRESS		FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/
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FILE 'HOME' ENTERED AT 16:29:56 ON 07 JUN 2006

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FILE 'EMBASE' ENTERED AT 16:30:08 ON 07 JUN 2006

=> s propranolol or 318-98-9 or 525-66-6
L1 176997 PROPRANOLOL OR 318-98-9 OR 525-66-6

=> s l1 and (cardiotoxic or cardiotoxicity)
L2 1232 L1 AND (CARDIOTOXIC OR CARDIOTOXICITY)

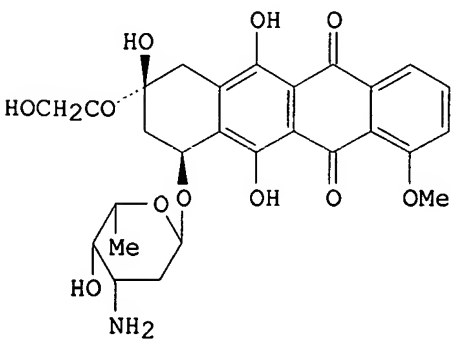
=> s l2 and (adriamycin or athracyclin or doxorubicin)
L3 74 L2 AND (ADRIAMYCIN OR ATHRACYCLIN OR DOXORUBICIN)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 55 DUP REM L3 (19 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L4
L5 55 FOCUS L4 1-

=> d ibib abs 1-55

L5 ANSWER 1 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:191374 CAPLUS
DOCUMENT NUMBER: 98:191374
TITLE: Verapamil, **propranolol**, and hydralazine protect against the acute cardiac depression induced by **adriamycin**
AUTHOR(S): Wikman-Coffelt, Joan; Rapcsak, Marianne; Sievers, Richard; Rouleau, Jean Lucien; Parmley, William W.
CORPORATE SOURCE: Cardiovasc. Res. Inst., Univ. California, San Francisco, CA, 94143, USA
SOURCE: Cardiovascular Research (1983), 17(1), 43-9
CODEN: CVREAU; ISSN: 0008-6363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The apex ejecting isolated rat heart perfused with media containing 3 +

10-5 mol/L **adriamycin** (I) [23214-92-8] for 40 min demonstrated the following changes in contraction patterns: (a) a 10-fold increase in end-diastolic pressure; (b) a 45% decrease in developed pressure; (c) a 17% decrease in coronary flow; (d) a 27% increase in time to peak pressure; (e) a 26% increase in time for pressure to fall 50% during relaxation; and (f) a 65% decrease in maximum (+) and (-) dP/dt. In rats pretreated 1 h before death, verapamil [52-53-9], **propranolol** [**525-66-6**], and hydralazine [86-54-4] significantly attenuated the cardiac depression produced by **adriamycin**. The combinations of verapamil and hydralazine, or **propranolol** and hydralazine were especially efficacious. Particularly striking was the protection afforded against an increase in diastolic pressure. digoxin [20830-75-5] Pretreatment afforded no protection. Apparently, acute depressive effects of **adriamycin** may be related to Ca overload.

L5 ANSWER 2 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1973:521795 CAPLUS
DOCUMENT NUMBER: 79:121795
TITLE: Positive chronotropic and inotropic actions of a new antitumor agent **adriamycin** and its **cardiotoxicity**. Myocardial contractile force and the change of the transmembrane action potential
AUTHOR(S): Kobayashi, Toshiji; Nakayama, Ryu; Takatani, Osamu; Kimura, Kiyoji
CORPORATE SOURCE: Dep. Intern. Med., Natl. Cancer Cent. Hosp., Tokyo, Japan
SOURCE: Japanese Circulation Journal (1972), 36(3), 259-65
CODEN: JCIRA2; ISSN: 0047-1828
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A single injection of 0.5-2.5 mg **adriamycin** (I) [23214-92-8]/0.1 ml into the isolated guinea pig heart perfused by Langendorff's technique produced pos. chronotropic and inotropic actions, and the acceleration of the repolarization process manifested by the shortening of the duration of the membrane action potential, especially the repolarization phase 2. I had a lesser degree of accumulative effect in producing arrhythmia than did daunomycin [20830-81-3]. The effects of I were completely blocked by DL-**propranolol** [13013-17-7].

L5 ANSWER 3 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1972:428821 CAPLUS
DOCUMENT NUMBER: 77:28821
TITLE: Prevention of the **cardiotoxic** effects of **adriamycin** and daunomycin in the isolated dog heart
AUTHOR(S): Herman, Eugene H.; Mhatre, Ramakant M.; Lee, Insu P.; Waravdekar, Vaman S.
CORPORATE SOURCE: Microbiol. Assoc., Inc., Bethesda, MD, USA
SOURCE: Proceedings of the Society for Experimental Biology and Medicine (1972), 140(1), 234-9
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Daunomycin (I) [20830-81-3] (50 mg) or **adriamycin** (II) [23214-92-8] (50 mg) perfused into the isolated dog heart increased coronary perfusion pressure. The increased pressure was not blocked by atropine sulfate, dl-**propranolol**-HCl, diphenhydramine-HCl or LSD. Pretreatment with disodium EDTA [139-33-3] (100 mg) or ICRF 159 [(+-)-1,2-bis(3,5-dioxopiperazin-1-yl)propane] [21416-87-5] (100 mg) prevented the increase in perfusion pressure induced by I or II and decreased the formation of their aglycone metabolites. The effect of I and II on the heart appears to be mediated by their aglycone metabolites. Possibly the removal of certain cations by EDTA and by ICRF 159 may be the cause of the altered metabolism and the reduced toxicity.

L5 ANSWER 4 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:115042 CAPLUS
DOCUMENT NUMBER: 88:115042
TITLE: Blockade of tissue uptake of the antineoplastic agent,

doxorubicin

AUTHOR(S): Somberg, John; Cagin, Norman; Levitt, Barrie; Bounous, Helene; Ready, Pedda; Leonard, Daniel; Anagnostopoulos, Constantine

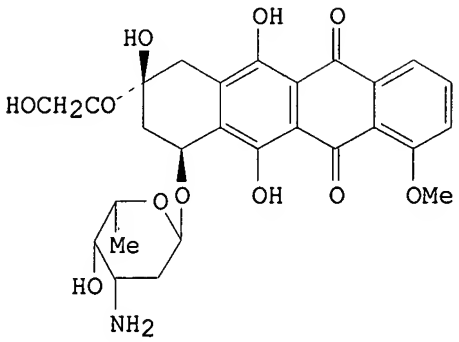
CORPORATE SOURCE: Dep. Med., New York Med. Coll., New York, NY, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1978), 204(1), 226-9
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Myocardial uptake of **doxorubicin** (**adriamycin**) (I) [23214-92-8] and its inhibition by digoxin [20830-75-5] and **propranolol** [**525-66-6**] were studied in paced, isolated perfused cat hearts using tritiated I. The myocardial content of I was 0.069 nmol/mg after 30 min. Combined administration of I and digoxin reduced the myocardial content of I to 0.025 nmol/mg. The combination increased contractility compared with I alone and increased coronary blood flow compared with digoxin alone. The reduction in the myocardial content of digoxin by I was not significant. **Propranolol** also reduced the myocardial uptake of I without changing coronary blood flow and without further reducing contractility. Thus, both **propranolol** and digoxin merit evaluation in preventing I **cardiotoxicity**.

L5 ANSWER 5 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:464294 CAPLUS

DOCUMENT NUMBER: 115:64294

TITLE: Effect of β-blocking agents on **cardiotoxicity** of anticancer drugs in guinea pigs

AUTHOR(S): Ahmed, Khwaja Zafar; Akkad, I. N. E. I.; Ikram-ul-Hak; Salim, Mohammed; Hussain, Waqar

CORPORATE SOURCE: Fac. Med., Al-Fateh University Medical Sciences, Tripoli, Libya

SOURCE: Pakistan Journal of Pharmacy (Lahore, Pakistan) (1989), 2(1-2), 27-33
CODEN: PAJPEN; ISSN: 1019-956X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Using the technique of digoxin induced cardiac arrhythmia, the effects of beta-blockers (practolol and **propranolol**), hydrocortisone sodium succinate and **cardiotoxic** anticancer drugs (cisplatin and **doxorubicin**) on death from digoxin in guinea pigs were investigated. **Cardiotoxicity** of anticancer drugs does not interfere with the **cardiotoxicity** of digoxin and that β-blockade does not have beneficial preventative effects on **cardiotoxicity**.

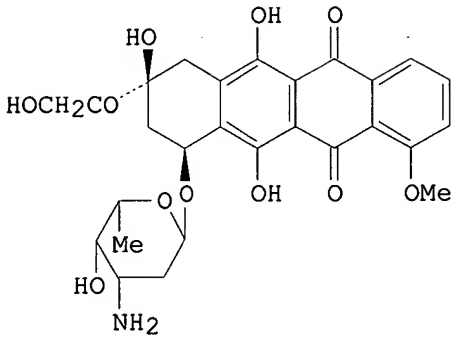
L5 ANSWER 6 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1980:597851 CAPLUS

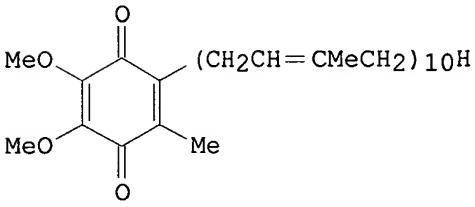
DOCUMENT NUMBER: 93:197851

TITLE: Protection against **doxorubicin**

cardiomyopathy in rabbits by coenzyme Q10: evidence for nonspecific myocardial preservation
AUTHOR(S): Bristow, Michael R.
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, USA
SOURCE: Biomed. Clin. Aspects Coenzyme Q, Proc. Int. Symp., 2nd (1980), Meeting Date 1979, 179-88. Editor(s): Yamamura, Yuichi; Folkers, Karl August; Ito, Y. Elsevier: Amsterdam, Neth.
CODEN: 44IYAO
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

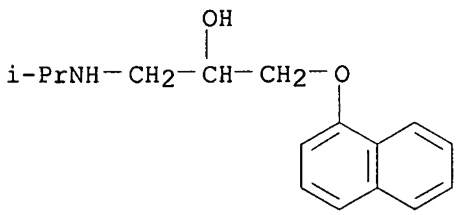


II

AB In rabbits, cardiomyopathy caused by **doxorubicin** (I) [23214-92-8] (2.0 and 2.5 mg/kg/wk, i.v.) was partially antagonized by high doses of the Ca antagonist verapamil [52-53-9], (1 mg/kg/12 h); this dose could not be tolerated >8 wk. Coenzyme Q10 (II) [303-98-0] offered partial protection in relatively short-term studies (<12 wk), and II and verapamil was more effective than II alone. α-Tocopheryl [59-02-9] had no effect on I cardiomyopathy. Histaminergic receptor blockade with diphenhydramine [58-73-1] and cimetidine [51481-61-9] or adrenergic blockade with phentolamine [50-60-2] and **propranolol** [**525-66-6**] conferred partial protection, whereas both histaminergic and adrenergic blockade, in combination conferred nearly total protection. Thus, I cardiomyopathy is mediated by vasoactive substances. Verapamil and II are probably acting non-specifically, and therefore may be useful in treatment of I cardiomyopathy.

L5 ANSWER 7 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:550366 CAPLUS
DOCUMENT NUMBER: 133:305432
TITLE: β-Blockade in **adriamycin**-induced cardiomyopathy
AUTHOR(S): Noori, Arshia; Lindenfeld, Joann; Wolfel, Eugene; Ferguson, Debbie; Bristow, Michael R.; Lowes, Brian D.
CORPORATE SOURCE: Division of Cardiology, Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, USA
SOURCE: Journal of Cardiac Failure (2000), 6(2), 115-119
CODEN: JCFAF9; ISSN: 1071-9164
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB β-Blockade consistently improves myocardial systolic function in

L2 ANSWER 104 OF 105 REGISTRY COPYRIGHT 2006 ACS on STN
RN 525-66-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)- (7CI, 8CI)
OTHER NAMES:
CN **(±)-Propranolol**
CN **β-Propranolol**
CN 1-(1-Naphthyloxy)-3-(isopropylamino)-2-propanol
CN 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol
CN AY 64043
CN Betalong
CN **dl-Propranolol**
CN **DL-Propranolol**
CN Euprovasin
CN Innopran XL
CN **Propranolol**
CN Proprasylyt
CN **Racemic propranolol**
CN Reducor
FS 3D CONCORD
DR 13013-17-7
MF C16 H21 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSPATENTS, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SCISEARCH, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11976 REFERENCES IN FILE CA (1907 TO DATE)
132 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12003 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 105 OF 105 REGISTRY COPYRIGHT 2006 ACS on STN
RN 318-98-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, hydrochloride (8CI)
OTHER NAMES:
CN **(±)-Propranolol hydrochloride**
CN **(R,S)-Propranolol hydrochloride**
CN 1-(1-Naphthoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride
CN 1-(1-Naphthyloxy)-2-hydroxy-3-isopropylaminopropane hydrochloride
CN 1-(1-Naphthyloxy)-3-(isopropylamino)-2-propanol hydrochloride

CN 1-(Isopropylamino)-3-(1-naphthoxy)-2-propanol hydrochloride
CN 1-(Isopropylamino)-3-(1-naphthyloxy)propan-2-ol hydrochloride
CN Anaprilin
CN Anapriline
CN Angilol
CN Apsolol
CN Avlocardyl
CN Bedranol
CN Beprane
CN Berkolol
CN Beta-Neg
CN Beta-Tablinen
CN Beta-Timelets
CN Cardinol
CN Caridolol
CN Deralin
CN DL-Anapriline
CN **dl-Propranolol hydrochloride**
CN **DL-Propranolol hydrochloride**
CN Docitan
CN Dociton
CN Duranol
CN Efektolol
CN Elbol
CN Frekven
CN ICI 45520
CN Inderal
CN Inderal LA
CN Indobloc
CN Intermigran
CN Kemi S
CN Naprilin
CN NSC 91523
CN Obsidan
CN Oposim
CN Prano-Puren
CN Prophylux
CN **Propranolol chloride**
CN **Propranolol hydrochloride**
CN Propranur
CN Propraratiopharm
CN Pylapron
CN Rapynogen
CN Sagittol
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 3506-09-0, 146874-86-4
MF C16 H21 N O2 . Cl H
CI COM
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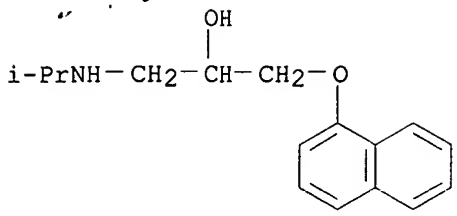
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (525-66-6)



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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2862 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2867 REFERENCES IN FILE CAPLUS (1907 TO DATE)
30 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

patients with both nonischemic and ischemic cardiomyopathy. The effects of β-blockade on **Adriamycin**-induced cardiomyopathy (ACM), however, are unknown. We retrospectively evaluated the effects of β-blockade on patients with ACM by using a case-controlled design. The control group consisted of 16 consecutively chosen age- and sex-matched patients with idiopathic dilated cardiomyopathy (IDC) who were treated with β-blockers. Patients with ACM had a baseline mean left ventricular ejection fraction (LVEF) of 28%, which improved to 41% (P = .041) after treatment with β-blockers. The control group had a baseline mean LVEF of 26%, which improved to 32% (P = .015) after treatment. The mean duration of β-blocker therapy in the **Adriamycin** and control groups was 8 and 9 mo, resp. The degree of improvement between the 2 groups was not significantly different. β-Blockers have a beneficial effect on cardiac function in patients with ACM, which is at least comparable with other forms of heart failure with systolic dysfunction.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:57553 CAPLUS
DOCUMENT NUMBER: 144:164658
TITLE: Differential cardioprotective/**cardiotoxic** effects mediated by β-adrenergic receptor subtypes
AUTHOR(S): Bernstein, Daniel; Fajardo, Giovanni; Zhao, Mingming; Urashima, Takashi; Powers, Jennifer; Berry, Gerald; Kobilka, Brian K.
CORPORATE SOURCE: Department of Pediatrics, Stanford University, Stanford, CA, USA
SOURCE: American Journal of Physiology (2005), 289(6, Pt. 2), H2441-H2449
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent data suggest that β-adrenergic receptor subtypes couple differentially to signaling pathways regulating cardiac function vs. cardiac remodeling. To dissect the roles of β1- vs. β2-receptors in the pathogenesis of cardiomyopathy, **doxorubicin** was administered to β1, β2, and β1/β2 knockout (-/-) and wild-type mice. Expression and activation of MAPKs were measured. Wild-type and β-/- mice showed no acute cardiovascular effects, whereas β2-/- mice all died within 30 min. The addnl. deletion of the β1-receptor (β1/β2-/-) totally rescued this toxicity. β2-/- Mice developed decreased contractile function, hypotension, QTc prolongation, and ST segment changes and a 20-fold increase in p38 MAPK activity not seen in the other genotypes. The MAPK inhibitor SB-203580 rescued β2-/- mice from this acute toxicity. The enhanced toxicity in β2-/- mice was also recapitulated in wild-type mice with the β2-selective antagonist ICI-118,551, although the rescue effect of the β1-deletion was not recapitulated using the β1-selective antagonist metoprolol or the nonselective β-antagonist **propranolol**. These data suggest that β2-adrenergic receptors play a cardioprotective role in the pathogenesis of cardiomyopathy, whereas β1-adrenergic receptors mediate at least some of the acute **cardiotoxicity** of anthracyclines. Differential activation of MAPK isoforms, previously shown in vitro to regulate β-agonist as well as **doxorubicin cardiotoxicity**, appears to play a role in mediating the differential effects of these β-adrenergic receptor subtypes in vivo.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 55 MEDLINE on STN

ACCESSION NUMBER: 85005810 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6480163
TITLE: Acute effects of **doxorubicin** (**adriamycin**) on left ventricular function in dogs.

AUTHOR: Ditchey R V; LeWinter M M; Higgins C B
CONTRACT NUMBER: 1K04HL00201 (NHLBI)
PHS-HL07444-01 (NHLBI)
PHS-HL24922 (NHLBI)
SOURCE: International journal of cardiology, (1984 Sep) Vol. 6, No. 3, pp. 341-53.
Journal code: 8200291. ISSN: 0167-5273.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 15 Nov 1984

AB Although chronic **doxorubicin** (**adriamycin**) **cardiotoxicity** often is attributed to repeated episodes of acute myocardial injury, the acute effects of **doxorubicin** on in vivo left ventricular performance have not been studied in a carefully controlled setting. Accordingly, we recorded high-fidelity left ventricular pressures and segmental dimensions before and after either intravenous or intracoronary **doxorubicin** in twelve open-chest dogs. **Propranolol** was administered to prevent reflex sympathetic stimulation, and heart rate was held constant by atrial pacing. Intravenous **doxorubicin** (1.5 mg/kg) (n = 6) caused significant decreases in all measured indices of myocardial contractility, in association with a large decrease in left ventricular systolic pressure (125 +/- 28 and 81 +/- 23 mm Hg before and 5 min after **doxorubicin** , respectively, P less than 0.01). Intracoronary **doxorubicin** (0.075 to 0.3 mg/kg) (n = 6) caused similar decreases in percent segment shortening (from 19 +/- 7 to 16 +/- 8, P less than 0.05), mean normalized shortening rate (from 0.87 +/- 0.34 to 0.71 +/- 0.37 segment lengths/sec, P less than 0.05), and peak positive left ventricular dP/dt (by 10 +/- 11%, P less than 0.07), although left ventricular systolic pressure was only modestly decreased (126 +/- 20 and 113 +/- 17 mm Hg before and after **doxorubicin**, respectively, P less than 0.01). Intracoronary **doxorubicin** also slowed the rate of left ventricular relaxation, as evidenced by an increase in the time constant for isovolumic pressure fall from 32.0 +/- 9.0 to 36.9 +/- 7.5 msec, and significantly altered the relationship between left ventricular pressure and dimension at end-diastole.

L5 ANSWER 10 OF 55 MEDLINE on STN
ACCESSION NUMBER: 2000285133 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10826857
TITLE: Effect of beta-blocker on metabolism and contraction of **doxorubicin**-induced **cardiotoxicity** in the isolated perfused rabbit heart.
AUTHOR: Kawabata H; Ryomoto T; Ishikawa K
CORPORATE SOURCE: First Department of Internal Medicine, Kinki University School of Medicine, Osaka-Sayama, Osaka, Japan.
SOURCE: Angiology, (2000 May) Vol. 51, No. 5, pp. 405-13.
Journal code: 0203706. ISSN: 0003-3197.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 16 Jun 2000
Last Updated on STN: 16 Jun 2000
Entered Medline: 6 Jun 2000

AB The effect of beta-blocker (**propranolol**) on the metabolism and contraction of **doxorubicin**-induced cardiomyopathy during pacing or ischemia was examined by the phosphorus 31-nuclear magnetic resonance (31 P-NMR) in Langendorff hearts of chronically treated rabbits after cumulative doses of 16 mg **doxorubicin**/kg. After 8 weeks of **doxorubicin** treatment, beta-blocker (**propranolol**) was given orally over a period of 2 weeks for a cumulative dose of 1.4 mg/kg. Isolated hearts were paced at higher heart rates, or hearts were perfused

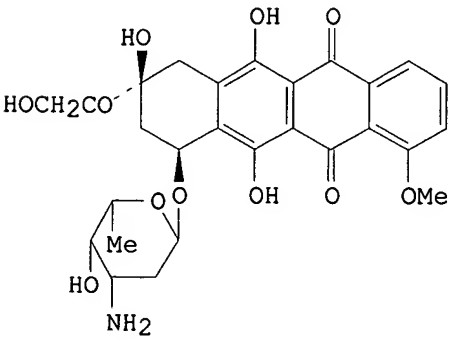
on low flow. Adenosine triphosphate (ATP), creatine phosphate (PCr), inorganic phosphate (Pi), pH, left ventricular systolic developed pressure (LVDev P), and coronary flow were measured. The hearts were divided into three experimental groups: Group I consisted of controls, Group II consisted of **doxorubicin** treatment, and Group III consisted of **doxorubicin** treatment with **propranolol**. Group II showed a significant decrease of ATP during pacing (48 +/- 2%) and during low flow (61 +/- 6%) compared with Group I (86 +/- 9% at pacing, 94 +/- 6% on low flow). But Group III showed a significantly marked improvement of ATP during pacing (95 +/- 10%) and during low flow (83 +/- 3%) compared with Group II. Furthermore, Group II showed a significant decrease of LVDev P during pacing (69 +/- 6 mm Hg) and during low flow (63 +/- 3 mm Hg) compared with Group I (101 +/- 5 mm Hg at pacing, 95 +/- 9 mm Hg on low flow). But Group III showed a significantly marked improvement of LVDev P during pacing (93 +/- 5 mm Hg) and during low flow (83 +/- 14 mm Hg) compared with Group II. In conclusion, **propranolol** had a significant beneficial effect on metabolism and contraction during high-energy demand and during low oxygen supply of **doxorubicin** cardiomyopathy.

L5 ANSWER 11 OF 55 MEDLINE on STN
ACCESSION NUMBER: 79034746 MEDLINE
DOCUMENT NUMBER: PubMed ID: 705032
TITLE: Potentiation of the toxicity of **adriamycin** by **propranolol**.
AUTHOR: Choe J Y; Combs A B; Folkers K
SOURCE: Research communications in chemical pathology and pharmacology, (1978 Sep) Vol. 21, No. 3, pp. 577-80. Journal code: 0244734. ISSN: 0034-5164.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197812
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 14 Mar 1990
Entered Medline: 27 Dec 1978
AB Both **propranolol** and **adriamycin** are biochemically known to inhibit mitochondrial CoQ10-enzymes of myocardial tissue in vitro. Both **propranolol** and **adriamycin** are clinically known to cause **cardiotoxicity**. At two dose levels of **propranolol** which caused no deaths to mice when administered alone, significant potentiation (p less than 0.01) of the lethality of **adriamycin** to mice was observed. These data, projected to the clinical situation, seem to contraindicate the administration of the beta-blocker, **propranolol**, for the hypertension of a cancer patient who is being treated with **adriamycin**.

L5 ANSWER 12 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:470872 CAPLUS
DOCUMENT NUMBER: 113:70872
TITLE: Isolated mouse atrium as a model to study anthracycline **cardiotoxicity**: the role of the β-adrenoceptor system and reactive oxygen species
AUTHOR(S): De Jong, J.; Schoofs, P. R.; Onderwater, R. C. A.; Van der Vijgh, W. J. F.; Pinedo, H. M.; Bast, A.
CORPORATE SOURCE: Dep. Oncol., Free Univ., Amsterdam, 1081 HV, Neth.
SOURCE: Research Communications in Chemical Pathology and Pharmacology (1990), 68(3), 275-89
CODEN: RCOCB8; ISSN: 0034-5164
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cancer chemotherapy with anthracyclines, of which **doxorubicin** (DX) is the main representative, is limited by cardiomyopathy developing in animals and patients after cumulative dosing. The toxicity is probably related to free radical formation by the anthracycline as well as its metabolites with concomitant O2- and OH generation resulting in lipid peroxidn. and subsequent membrane damage. Isolated mouse atrium was

chosen as an in vitro model to investigate the individual contribution of each metabolite to **cardiotoxicity**, since the mouse lacks the DX-induced nephrotic syndrome seen for instance in rats and rabbits. To characterize the model, l-isoprenaline/dl-propanolol and metacholine/atropine were used to measure the β-adrenergic and the muscarinic responses of (spontaneously beating) right and (paced) left atrium. Dose response curves were highly reproducible: pD2,iso = 8.0 (left) and 8.5 (right); pD2,met = 6.7 (left) and 6.2 (right). **Propranolol** as well as atropine behaved as competitive antagonists, with pA2-values of 8.4/8.5 (l/r) and 9.1/9.1 (l/r), resp. These values corresponded to those obtained with other organ prepns. The effect of DX was tested in two ways: a) by measuring the direct inotropic and chronotropic effect during 60 min of incubation with 10-100 μM DX in the organ bath, and b) by determining the remaining β-adrenergic response to l-isoprenaline after the incubation period. Both variables turned out to be equally affected. For paced left atria an IC50 (causing 50% depression of contractile force) of 35 μM was determined Right atria stopped beating at concns. above 50 μM, thus hampering IC50 determination The results indicate that anthracyclines exert an effect not related to receptor integrity, but directly to the functionality of heart muscle. The check whether radical stress can be involved in the observed neg. inotropic effect, incubations with xanthine/xanthine involved in the observed neg. inotropic effect, incubations with xanthine/xanthine oxidase (to produce reactive oxygen species) were performed. A pronounced neg. effect on mouse atrial contraction was indeed observed However, initially a pos. inotropic effect accompanied by an increased resting tension was seen. Thus, mouse atrium can be used as a model to compare anthracyclines and their metabolites with regard to their acute **cardiotoxic** effects.

L5 ANSWER 13 OF 55 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:527025 CAPLUS
DOCUMENT NUMBER: 87:127025
TITLE: Inhibition of cardiac CoQ10-enzymes by clinically used drugs and possible prevention
AUTHOR(S): Kishi, Takeo; Kishi, Hiroe; Folkers, Karl
CORPORATE SOURCE: Sch. Pharm., Kobe-Gakuin Univ., Kobe, Japan
SOURCE: Biomed. Clin. Aspects Coenzyme Q, Proc. Int. Symp. (1977), Meeting Date 1976, 47-62. Editor(s): Folkers, Karl; Yamamura, Yuichi. Elsevier: Amsterdam, Neth. CODEN: 36EXA4
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

AB Of 5 antitumor drugs tested, **adriamycin** (I) [23214-92-8] caused the greatest inhibition of the isolated heart mitochondria CoQ10-dependent enzymes, succinoxidase [9014-35-1] and NADH oxidase [9032-21-7]. Daunomycin [20830-81-3] and mitomycin C [50-07-7] were less inhibitory, and the nonquinones cyclophosphamide [50-18-0] and 5-fluorouracil [51-21-8] caused little or no inhibition. Lipoidal 14-acyl derivs. of I such as I 14-octanoate [42077-25-8] were more inhibitedly than I. The inhibition was prevented by CoQ10 and to a lesser extent by its lower

homologs. Among 8 antihypertensives tested, diazoxide [364-98-7] and methyldopa [555-30-6] inhibited only succinoxidase, whereas **propranolol** [**525-66-6**], metoprolol [37350-58-6], hydralazine [86-54-4], clonidine [4205-90-7], and hydrochlorothiazide [58-93-5] inhibited only NADH oxidase; reserpine [50-55-5] inhibited neither enzyme. The mechanism of inhibition by the nonquinonoid antihypertensives may be different from that by the quinonoid antitumor agents. The inhibition may be related to the **cardiotoxicity** of these agents.

L5 ANSWER 14 OF 55 EMBASE

ACCESSION NUMBER: 2004366809 EMBASE
TITLE: [**Cardiotoxicity** of antitumorous treatment]. KARDIOTOXICITA PROTINADOROVE LECBY.
AUTHOR: Horacek J.; Pudil R.; Tichy M.; Jebavy L.; Slovacek L.
CORPORATE SOURCE: Dr. J. Horacek, Kat. Valecneho Vnitrniho Lekarstvi, Vojenske Lekarske Akad. J.E. Purkyne, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic
SOURCE: Transfuze a Hematologie Dnes, (2004) Vol. 10, No. 2, pp. 62-69. .
Refs: 35
ISSN: 1213-5763 CODEN: THDRAK
COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Czech
SUMMARY LANGUAGE: Czech; English
ENTRY DATE: Entered STN: 16 Sep 2004
Last Updated on STN: 16 Sep 2004

AB **Cardiotoxicity** is a serious and relatively frequent complication in patients treated for cancer. Antitumorous treatment can cause a number of undesirable cardiac side effects, such as arrhythmias, myocardial ischaemia, sudden death and heart failure. **Cardiotoxicity** can manifest anytime during treatment and anytime after its termination. Late **cardiotoxicity** of anthracyclines, which can manifest as chronic heart failure more than one year after termination of the treatment, is one of the most serious problems. In view of indisputable success of antitumorous treatment recently, the issue of **cardiotoxicity** becomes more and more relevant. The authors review the most frequent cardiac complications of antitumorous treatment. They emphasize the **cardiotoxicity** of anthracyclines and its derivatives, because they represent the greatest risk. Furthermore, they review the cardiotoxity of other cytostatics, immunomodulators, radiotherapy and cardiac complications associated with transplantation of haematopoietic cells.

L5 ANSWER 15 OF 55 MEDLINE on STN

ACCESSION NUMBER: 2005015506 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15641294
TITLE: Advantages in the use of carvedilol versus **propranolol** for the protection of cardiac mitochondrial function.
AUTHOR: Oliveira Paulo J; Rolo Anabela P; Sardao Vilma A; Monteiro Pedro; Goncalves Lino; Providencia Luis A; Palmeira Carlos M; Moreno Antonio J M
CORPORATE SOURCE: Centro de Neurociencias e Biologia Celular de Coimbra, Departamento de Zoologia, Universidade de Coimbra, Coimbra, Portugal.. pauloliv@ci.uc.pt
SOURCE: Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology, (2004 Oct) Vol. 23, No. 10, pp. 1291-8.
Journal code: 8710716. ISSN: 0870-2551.
PUB. COUNTRY: Portugal
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 12 Jan 2005
Last Updated on STN: 18 May 2005
Entered Medline: 17 May 2005

AB BACKGROUND: Carvedilol is a neurohormonal antagonist of multiple action which is used in clinical practice for the treatment of congestive heart failure, mild to moderate hypertension and myocardial infarction. Previous results from our group have demonstrated that one of the main targets for the protective effect of carvedilol is the cardiac mitochondrial network. In-this work, we compare the effect of carvedilol with **propranolol** in different models of mitochondrial dysfunction and in the generation of transmembrane electric potential (EP). We further tested if carvedilol was able to inhibit the mitochondrial permeability transition (MPT) induced by **doxorubicin** and calcium-dependent cytochrome c release, a phenomenon frequently associated with apoptotic cell death. METHODS: Cardiac mitochondria were isolated by differential centrifugation. Oxygen consumption and mitochondrial EP were determined using an oxygen electrode and a tetraphenylphosphonium-sensitive electrode, respectively. Changes in mitochondrial volume and the release of cytochrome c were measured with spectrophotometric techniques. RESULTS: **Propranolol**, compared with carvedilol, had only a marginal effect, not only in protection against MPT induction, but also against oxygen consumption linked to the oxidation of external NADH, a process that is considered by several authors as key in the **cardiotoxicity** of **doxorubicin**. Regarding EP generation, **propranolol** had no effect, in contrast to carvedilol, which was confirmed to act as a protonophore. For the first time we also show that carvedilol inhibits the MPT induced by **doxorubicin** and calcium-dependent cytochrome c release. CONCLUSIONS: With this work, we further support the notion that carvedilol is effective in several models of mitochondrial dysfunction, particularly those involving oxidative stress. The results demonstrate that for some pathological conditions, carvedilol and **propranolol** have different mechanisms of action at the sub-cellular level, as **propranolol** seems to lack effectiveness in the protection of cardiac mitochondria.

L5 ANSWER 16 OF 55 EMBASE

ACCESSION NUMBER: 2005538991 EMBASE
TITLE: Differential cardioprotective/**cardiotoxic** effects mediated by β-adrenergic receptor subtypes.
AUTHOR: Bernstein D.; Fajardo G.; Zhao M.; Urashima T.; Powers J.; Berry G.; Kobilka B.K.
CORPORATE SOURCE: D. Bernstein, Dept. of Pediatrics, 750 Welch Rd., Palo Alto, CA 94304, United States. danb@stanford.edu
SOURCE: American Journal of Physiology - Heart and Circulatory Physiology, (2005) Vol. 289, No. 6 58-6, pp. H2441-H2449. .
Refs: 36
ISSN: 0363-6135 CODEN: AJPPDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 2005
Last Updated on STN: 29 Dec 2005

AB Recent data suggest that β-adrenergic receptor subtypes couple differentially to signaling pathways regulating cardiac function vs. cardiac remodeling. To dissect the roles of β1- vs. β2-receptors in the pathogenesis of cardiomyopathy, **doxorubicin** was administered to β1, β2, and β1/β2 knockout ((-/-)) and wild-type mice. Expression and activation of MAPKs were measured. Wild-type and β1 (-/-) mice showed no acute cardiovascular effects, whereas β2 (-/-) mice all died within 30 min. The additional deletion of the β1-receptor

(β1/β2(-/-)) totally rescued this toxicity. β2(-/-) mice developed decreased contractile function, hypotension, QTc prolongation, and ST segment changes and a 20-fold increase in p38 MAPK activity not seen in the other genotypes. The MAPK inhibitor SB-203580 rescued β2(-/-) mice from this acute toxicity. The enhanced toxicity in β2(-/-) mice was also recapitulated in wild-type mice with the β2-selective antagonist ICI-118,551, although the rescue effect of the β1-deletion was not recapitulated using the β1-selective antagonist metoprolol or the nonselective β-antagonist **propranolol**. These data suggest that β2-adrenergic receptors play a cardioprotective role in the pathogenesis of cardiomyopathy, whereas β1-adrenergic receptors mediate at least some of the acute **cardiotoxicity** of anthracyclines. Differential activation of MAPK isoforms, previously shown in vitro to regulate β-agonist as well as **doxorubicin cardiotoxicity**, appears to play a role in mediating the differential effects of these β-adrenergic receptor subtypes in vivo. .COPYRGT. 2005 the American Physiolosical Society.

L5 ANSWER 17 OF 55 EMBASE

ACCESSION NUMBER: 90262211 EMBASE
DOCUMENT NUMBER: 1990262211
TITLE: Cardiovascular effects of **doxorubicin**.
AUTHOR: Tsai C.S.; Washington C.; Ochillo R.F.
CORPORATE SOURCE: Laboratory of Pharmacology, Biomedical Research Center, Xavier Univ. of Louisiana,New Orleans, LA 70125, United States
SOURCE: General Pharmacology, (1990) Vol. 21, No. 5, pp. 729-733. . ISSN: 0306-3623 CODEN: GEPHDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Dec 1991
Last Updated on STN: 13 Dec 1991

AB **Doxorubicin** dose-dependently increased the cardiac contractility of isolated frog heart within the dose-range of 1.0 to 10.0 x 10-7 M and dose-dependently increased the cardiac output of frog heart in situ with a dose-range between 10-7 and 10-5 M. The results of the in situ investigation, using cardiac output as the index of cardiac contractility, were in agreement with the in vitro results. The positive inotropic effects of **doxorubicin** climaxed around 10-5 M beyond which there was a dose-dependent decreased in contractility. Haloperidol (10-6 M), a dopaminergic receptor blocker, and **propranolol** (10-8 M), a β-adrenergic blocker, did not block the positive inotropic effects of **doxorubicin**. These results provide sufficient basis to suggest that **doxorubicin** is acting on the isolated amphibian heart through a mechanism which is not associated with β-adrenergic and/or dopaminergic receptors.

L5 ANSWER 18 OF 55 EMBASE

ACCESSION NUMBER: 1998256452 EMBASE
TITLE: Anthracycline-induced **cardiotoxicity**.
AUTHOR: Shan K.; Lincoff A.M.; Young J.B.
CORPORATE SOURCE: Dr. A.M. Lincoff, Experimental Interventional Lab., Department of Cardiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States
SOURCE: Annals of Internal Medicine, (1996) Vol. 125, No. 1, pp. 47-58. .
Refs: 146
ISSN: 0003-4819 CODEN: AIMEAS
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine

018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Aug 1998
Last Updated on STN: 20 Aug 1998

AB Purpose: To review the current understanding of the clinical significance, detection, pathogenesis, and prevention of anthracycline- induced **cardiotoxicity**. Data Sources: A MEDLINE search of the English-language medical literature and a manual search of the bibliographies of relevant articles, including abstracts from national cardiology meetings. Study Selection: Pertinent clinical and experimental studies addressing the clinical relevance, pathogenesis, detection, and prevention of anthracycline **cardiotoxicity** were selected from peer-reviewed journals without judgments about study design. A total of 137 original studies and 9 other articles were chosen. Data Extraction: Data quality and validity were assessed by each author independently. Statistical analysis of combined data was inappropriate given the differences in patient selection, testing, and follow-up in the available studies. Data Synthesis: Anthracyline-induced **cardiotoxicity** limits effective cancer chemotherapy by causing early cardiomyopathy, and it can produce late-onset ventricular dysfunction years after treatment has ceased. Detection of subclinical anthracyline-induced cardiomyopathy through resting left ventricular ejection fraction or echocardiographic fractional shortening is suboptimal. Conventional doses of anthracycline often lead to permanent myocardial damage and reduced functional reserve. Underlying pathogenetic mechanisms may include free-radical-mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and the release of **cardiotoxic** cytokines. Dexrazoxane is the only cardioprotectant clinically approved for use against anthracyclines, and it was only recently introduced for selected patients with breast cancer who are receiving anthracycline therapy. Conclusions: A rapidly growing number of persons, including an alarming fraction of the 150 000 or more adults in the United States who have survived childhood cancer, will have substantial morbidity and mortality because of anthracycline-related cardiac disease. The development of effective protection against anthracycline-induced **cardiotoxicity** will probably have a significant effect on the overall survival of these patients.

L5 ANSWER 19 OF 55 EMBASE

ACCESSION NUMBER: 78382465 EMBASE
DOCUMENT NUMBER: 1978382465
TITLE: Subclinical **adriamycin cardiotoxicity**: detection by timing the arterial sounds.
AUTHOR: Greco F.A.
CORPORATE SOURCE: Dept. Med., Vanderbilt Univ. Med. Cent., Nashville, Tenn., United States
SOURCE: Cancer Treatment Reports, (1978) Vol. 62, No. 6, pp. 901-905. .
CODEN: CTRRDO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
025 Hematology
LANGUAGE: English

AB 'Sphygmo-Recording', a noninvasive method for timing the arterial pulse wave contour, provides a measurement (QK(d) interval) which reflects changes in myocardial contractility and stroke output. The QK(d) interval, ie, the time between the onset of the QRS complex (Q) and the onset of the Korotkoff sounds (K) at the brachial artery at diastolic pressure (d), is the sum of the cardiac pre-ejection period and the pulse transmission time. Serial QK(d) intervals were done in patients receiving

adriamycin (ADM) alone, in sequence with other chemotherapy, in combination chemotherapy, and in combination with radiotherapy. The QK(d) interval was significantly prolonged (>30 msec) within 1-3 weeks after ADM therapy alone or in combination therapy in >50% of patients after the first dose and subsequently. Although similar changes were seen in patients receiving ADM in combination with cyclophosphamide, vincristine, and mediastinal radiotherapy, these patients often showed repeated and sustained QK(d) elevations. The QK(d) interval returned to baseline in most patients 2-4 months after stopping ADM. Four of seven patients receiving >550 mg/m2 of ADM developed congestive heart failure. In three patients, the QK(d) interval failed to return to baseline values during ADM therapy 1-3 months prior to any other evidence of heart failure. In the fourth patient, ADM was stopped prior to heart failure after the QK(d) failed to return toward baseline levels; the QK(d) returned to normal for 4 months but abruptly increased in association with severe congestive heart failure. The QK(d) interval appears to reflect subclinical ADM **cardiotoxicity**. Although weekly serial QK(d) measurements may be useful in more accurately predicting clinical cardiomyopathy in patients receiving >550 mg/m2, it is not specific nor absolutely reliable.

L5 ANSWER 20 OF 55 EMBASE

ACCESSION NUMBER: 80109662 EMBASE
DOCUMENT NUMBER: 1980109662
TITLE: Sudden death during **doxorubicin** administration.
AUTHOR: Wortman J.E.; Lucas Jr. V.S.; Schuster E.; et al.
CORPORATE SOURCE: Dept. Med., Duke Univ. Med. Cent., Durham, N.C. 27710, United States
SOURCE: Cancer, (1979) Vol. 44, No. 5, pp. 1588-1591. .
CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
030 Pharmacology
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB Three patients are described who either died suddenly or had severe, lifethreatening arrhythmias during or immediately after **doxorubicin** administration. Since **doxorubicin** and daunorubicin administration is known to be associated with acute EKG abnormalities, the acute decompensation in these patients appeared to be caused by the administration of these agents. The importance of careful observation of patients receiving **doxorubicin**, because of the possibility of acute cardiac arrhythmias, is stressed.

L5 ANSWER 21 OF 55 EMBASE

ACCESSION NUMBER: 2001080315 EMBASE
TITLE: High-dose mitoxantrone + melphalan (MITO/L-PAM) as conditioning regimen supported by peripheral blood progenitor cell (PBPC) autograft in 113 lymphoma patients: High tolerability with reversible **cardiotoxicity**.
AUTHOR: Tarella C.; Zallio F.; Caracciolo D.; Cuttica A.; Corradini P.; Gavarotti P.; Ladetto M.; Podio V.; Sargiotto A.; Rossi G.; Gianni A.M.; Pileri A.
CORPORATE SOURCE: C. Tarella, Cattedra di Ematologia, Via Genova 3, 10126 Torino, Italy
SOURCE: Leukemia, (2001) Vol. 15, No. 2, pp. 256-263. .
Refs: 50
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 2001
Last Updated on STN: 16 Mar 2001

AB Hematological and extrahematological toxicity of high-dose (hd) mitoxantrone (MITO) and melphalan (L-PAM) as conditioning regimen prior to peripheral blood progenitor cell (PBPC) autograft was evaluated in 113 lymphoma patients (87 at disease onset). Autograft was the final part of a hd-sequential (HDS) chemotherapy program, including a debulkying phase (1-2 APO ±2 DHAP courses) and then sequential administration of hd-cyclophosphamide, methotrexate (or Ara-C) and etoposide, at 10 to 30 day intervals. Autograft phase included: (1) hd-MITO, given at 60 mg/m(2) on day -5; (2) hd-L-PAM, given at 180 mg/m(2) on day -2; (3) PBPC autograft, with a median of 11 x 10(6) CD34(+)/kg, or 70 x 10(4) CFU-GM/kg, on day 0. A rapid hematological recovery was observed in most patients, with ANC >500/μL and Plt >20 000/μI values reached at a median of 11 and 10 days since autograft, respectively. The good hemopoietic reconstitution allowed the delivery of consolidation radiotherapy (RT) to bulky sites in 53 out of 57 candidate patients, within 1 to 3 months following autograft; five of these patients required back-up PBPC re-infusion due to severe post-RT pancytopenia. Few severe infectious complications were recorded. There was one single fatal event due to severe pancytopenia following whole abdomen RT. Cardiac toxicity was evaluated as left ventricular ejection fraction (LVEF), monitored by cardiac radionuclide scan. LVEF prior to and after autograft was significantly reduced (median values: 55% vs 46%) in 58 evaluated patients; however, a significant increase to a median value of 50% was observed in 45 patients evaluated at 1 to 3 years since autograft. At a median follow-up of 3.6 years, 92 patients are alive, with a 7-year overall survival projection and 6.7-year failure-free survival projection of 77% and 69%, respectively. We conclude that a conditioning regimen with hd-MITO/L-PAM fits well within the HDS program. It implies good tolerability and reversible **cardiotoxicity** and it may have contributed to the good long-term outcome observed in this series of patients.

L5 ANSWER 22 OF 55 EMBASE
ACCESSION NUMBER: 83037979 EMBASE
DOCUMENT NUMBER: 1983037979
TITLE: Toxic cardiomyopathy due to **doxorubicin**.
AUTHOR: Bristow M.R.
CORPORATE SOURCE: Stanford Univ., Stanford, CA, United States
SOURCE: Hospital Practice, (1982) Vol. 17, No. 12, pp. 101-111. .
CODEN: HOPRBW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
052 Toxicology
018 Cardiovascular Diseases and Cardiovascular Surgery
016 Cancer
030 Pharmacology
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB The use of **doxorubicin** poses a clinical dilemma: This effective antitumor agent is also high **cardiotoxic**. Thus, cardiac failure has been all too common in patients whose cancers have been controlled. A protocol based on identification and monitoring of patients with certain risk factors permits chemotherapy with little cardiac morbidity and virtually no mortality from drug-induced congestive failure.

L5 ANSWER 23 OF 55 EMBASE
ACCESSION NUMBER: 81236888 EMBASE

DOCUMENT NUMBER: 1981236888
TITLE: Anthracycline-associated cardiac and renal damage in rabbits. Evidence for mediation by vasoactive substances.
AUTHOR: Bristow M.R.; Minobe W.A.; Billingham M.E.; et al.
CORPORATE SOURCE: Dept. Med., Stanford Univ. Sch. Med., Stanford, Calif. 94305, United States
SOURCE: Laboratory Investigation, (1981) Vol. 45, No. 2, pp. 157-168. .
CODEN: LAINAW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB We tested the hypothesis that anthracycline-induced cardiac and renal damage is mediated by vasoactive substances. A 1-minute exposure to 5 μg. per ml. of **doxorubicin** (DXR, **Adriamycin**) produced cardiac histamine release in isolated rabbit hearts. Under conditions in which histamine uptake and metabolism were impaired, the administration of DXR, 2 mg. per kg., over 1 minute was associated with elevations in arterial histamine and catecholamines. The chronic weekly administration of DXR produced severe cardiac and renal damage. The administration of combined histaminic and adrenergic blockade with diphenhydramine, cimetidine, phentolamine, and **propranolol** (DCPP) pre- and immediately post-DXR resulted in near total protection against DXR-mediated cardiac damage and prevented the majority of the renal lesions. The combined administration of diphenydramine, cimetidine, phentolamine, and propranol did not appear to be acting by mechanisms other than blockade of vasoactive amine receptors as cardiac uptake of DXR and the DXR antitumor response were not altered by diphenhydramine, cimetidine, phentolamine, and **propranolol**. This study demonstrates that anthracycline-associated cardiac and renal toxicity may be mediated by vasoactive substances and that anthracycline cardiomyopathy is potentially preventable.

L5 ANSWER 24 OF 55 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1982:261632 BIOSIS
DOCUMENT NUMBER: PREV198274034112; BA74:34112
TITLE: ELECTRO PHYSIOLOGICAL STUDY OF EFFECTS OF COENZYME Q-10 UPON IMPAIRED MYO CARDIUM.
AUTHOR(S): FURUKAWA K [Reprint author]
CORPORATE SOURCE: SECOND DEP INTERNAL MED, KYOTO PREFECTURAL UNIV MED
SOURCE: Journal of Kyoto Prefectural University of Medicine, (1982) Vol. 91, No. 1, pp. 27-40.
CODEN: KFIZAO. ISSN: 0023-6012.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: JAPANESE

AB Coenzyme Q10 (CoQ10), isolated from the electron transfer system in the mitochondria, was reported to produce the favorable protective and restorative effect on the myocardium impaired with ischemia or **cardiotoxic** drugs such as **adriamycin** (ADR) in both clinical and experimental studies. The mechanism of action of CoQ10 was investigated in the isolated cardiac muscles impaired with ADR and 2,4-dinitrophenol (DNP). The right papillary muscles of guinea pig (200-250 g) were isolated from the animals and perfused with Tyrode solution (37° C) at 8 ml/min. The isometric contractions of the muscles were induced by stimulating electrically at 1 Hz, and action potentials were studied by intracellular microelectrode technique. ADR (0.3-2.0 μg/ml) exhibited dose-dependent negative inotropic action, which was not affected by atropine (5 + 10-7 M). Addition of CoQ10 (100 μg/ml) restored the myocardial contractility impaired by ADR (2

μg/ml). The restoration of CoQ10 to the ADR-induced impairment of contractility was also induced by β-blocker (**propranolol**, 5 + 10-6 M) or H2-blocker (metiamide, 2 + 10-6 M). This restorative effect of CoQ10 was partially inhibited by indomethacin (an inhibitor of fatty acid cyclooxygenase, 5 mg/kg) injected i.v. 20 min prior to isolation of the cardiac muscles. Exogenous CoQ10 apparently restores the ADR-induced impairment of the contractile activity and the action of CoQ10 may be mediated by the release of prostaglandin(PG)-like substances from the cardiac tissue treated by ADR. This hypothesis was tested by studying the action of CoQ10 on the papillary muscles treated by DNP which is an uncoupler in electron transfer system. The isolated papillary muscles were perfused with high K+ (27 mM) Tyrode solution at a similar condition, and were depolarized to about -40 mV in resting potentials. Addition of isoproterenol (3 + 10-8 M) restored the electrical slow action potentials and contractions. Administration of DNP (6 + 10-6 M) depressed the slow action potentials and contractions and abolished them within 60 min. Additional application of CoQ10 rapidly restored them. This restorative action of CoQ10 was not observed in the preparation pretreated with indomethacin and in the addition of 15-hydroperoxy arachidonic acid (10 μg/ml) which is an inhibitor of prostacyclin (PGI2) synthetase. The administration of exogenous CoQ10 is useful in the treatment of cardiac dysfunction. CoQ10 could affect the release of PG, especially PGI2, from cardiac tissue. In the mechanism of action of CoQ10 associated with PGI2, it is postulated that CoQ10 participates in scavenging the free radicals produced in arachidonic acid cascade and in inhibiting PGI2 synthetase.

L5 ANSWER 25 OF 55 EMBASE

ACCESSION NUMBER: 86225523 EMBASE
DOCUMENT NUMBER: 1986225523
TITLE: Effects of chronic administration of **doxorubicin** on myocardial beta-adrenergic receptors.
AUTHOR: Robison T.W.; Giri S.N.
CORPORATE SOURCE: Department of Veterinary Pharmacology and Toxicology, Shool of Veterinary Medicine, University of California, Davis, CA 95616, United States
SOURCE: Life Sciences, (1986) Vol. 39, No. 8, pp. 731-736. .
CODEN: LIFSAK
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
023 Nuclear Medicine
052 Toxicology
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB The effects of multiple doses of **doxorubicin** (DXR) on myocardial β-adrenergic receptor density and dissociation constant were investigated in male Sprague Dawley rats. The rats received DXR (2 mg/kg) or vehicle weekly by the SC route for 13 weeks. One group of DXR-treated rats plus corresponding controls were sacrificed at 14 weeks, one week after the last dose. Another group of DXR-treated rats plus corresponding controls were sacrificed at 19 weeks, six weeks after the last dose. The myocardial β-adrenergic receptor was characterized by radio-ligand binding studies using [125I]iodocyanopindolol. Beta-receptor densities in DXR-treated rats of 7.0 and 7.4 fm/mg protein were unchanged from control levels of 7.2 fm/mg protein at both 14 and 19 weeks, respectively. Receptor dissociation constants in DXR-treated rats of 36.7 and 36.9 pM were increased over control levels of 24.6 and 30.0 pM at 14 and 19 weeks, respectively. However, the change in dissociation constant is only significant at 14 weeks. The increased dissociation constants suggest diminished agonist binding affinity of the myocardial β-receptor. This impaired response of the receptor to catecholamines would tend to diminish the ability of myocardium to adequately respond to adrenergic stimuli.

L5 ANSWER 26 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 81166485 EMBASE
DOCUMENT NUMBER: 1981166485
TITLE: Direct and noninvasive evaluation of the cardiovascular response to isometric exercise.
AUTHOR: Perez-Gonzales J.F.; Schiller N.B.; Parmley W.W.
CORPORATE SOURCE: Cardiovasc. Div., Dept. Med., Univ. California, San Francisco, Calif. 94143, United States
SOURCE: Circulation Research, (1981) Vol. 48, No. 6 II, pp. I-138-I-148. .
CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
019 Rehabilitation and Physical Medicine
035 Occupational Health and Industrial Medicine
002 Physiology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB One method for testing cardiac reserve is to increase arterial pressure by isometric handgrip exercise (IHE) which increases the afterload against which the left ventricle must eject blood. In previous invasive studies in patients with cardiac disease, decreased ventricular reserve during IHE was manifest by a marked rise in LVEDP and a fall in cardiac output and stroke work index. To avoid the limitations of invasive techniques, we used M-mode echocardiography and other noninvasive measurements to evaluate the response to IHE in 11 normals and four patients with varying degrees of **adriamycin cardiotoxicity**. The normal response to IHE was manifest by an increase in heart rate (38%), arterial pressure (40%), cardiac output (53%), left ventricular end-diastolic diameter (12%), and end-systolic diameter (6%). There was no essential change in systemic vascular resistance, fractional shortening, or ejection fraction. In five normal subjects, 2 hours after 80 mg of oral **propranolol**, the response to IHE was altered as follows. Although the rise in arterial pressure was the same, the heart rate increase was blunted, and there was no significant rise in cardiac output. In the **adriamycin**-treated group the resting heart rate was higher, but the blood pressure response to IHE was the same. Compared to the normals, the **adriamycin** group had a fall in VCF and a rise in fractional shortening and ejection fraction, together with a rise in end-systolic diameter. Although further studies must be performed, noninvasive characterization of IHE may be helpful in evaluating ventricular reserve.

L5 ANSWER 27 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 79185133 EMBASE
DOCUMENT NUMBER: 1979185133
TITLE: Demonstration that **adriamycin cardiotoxicity** is mediated by vasoactive amines.
AUTHOR: Bristow M.R.; Billingham M.E.; Minobe W.A.; et al.
CORPORATE SOURCE: Dept. Med. Pathol., Stanford Univ., Stanford, Calif., United States
SOURCE: Journal of Molecular and Cellular Cardiology, (1979) Vol. 11, No. 1 SUPPL., pp. 10. .
CODEN: JMCDAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 28 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 79183880 EMBASE
DOCUMENT NUMBER: 1979183880

TITLE: Histamine and catecholamines mediate **adriamycin cardiotoxicity**.
AUTHOR: Bristow M.R.; Billingham M.E.; Daniels J.R.
CORPORATE SOURCE: Stanford Univ. Med. Cent., Stanford, Calif. 94305, United States
SOURCE: Proceedings of the American Association for Cancer Research, (1979) Vol. Vol. 20, pp. No. 477. .
CODEN: PAACA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 29 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 77160059 EMBASE
DOCUMENT NUMBER: 1977160059
TITLE: **Cardiotoxicity** of **adriamycin** and related anthracyclines.
AUTHOR: Lenaz L.; Page J.A.
CORPORATE SOURCE: Adria Lab. Inc., Wilmington, Del. 19899, United States
SOURCE: Cancer Treatment Reviews, (1976) Vol. 3, No. 3, pp. 111-120. .
CODEN: CTREDJ
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
030 Pharmacology
006 Internal Medicine
LANGUAGE: English
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 30 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005203295 EMBASE
TITLE: Are the antioxidant properties of carvedilol important for the protection of cardiac mitochondria?.
AUTHOR: Oliveira P.J.; Goncalves L.; Monteiro P.; Providencia L.A.; Moreno A.J.
CORPORATE SOURCE: L. Goncalves, Basic Research Unit in Cardiology, Cardiology Department, Coimbra University Hospital, P-3000-075 Coimbra, Portugal. lgoncalv@ci.uc.pt
SOURCE: Current Vascular Pharmacology, (2005) Vol. 3, No. 2, pp. 147-158. .
Refs: 114
ISSN: 1570-1611 CODEN: CVPUAY
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2005
Last Updated on STN: 19 May 2005
AB The cellular role of mitochondria includes ATP generation and the modulation of cytosolic calcium signals, besides being the "crossroads" for several cell death pathways. The maintenance of optimal mitochondrial functioning during the disease process increases the chances for survival. For example, ischaemia followed by reperfusion is known to negatively affect mitochondrial function, namely by inducing a deleterious condition called mitochondrial permeability transition (MPT). The MPT is responsible for mitochondrial dysfunction and can ultimately lead to cell

death. Therefore, it seems important to protect mitochondrial function in cardiac disease. Carvedilol, a β-adrenergic receptor antagonist with antioxidant properties, has a positive impact on cardiac mitochondria during in vitro, ex-vivo and in vivo models of cardiac dysfunction. Particularly, carvedilol was shown to inhibit MPT in isolated heart mitochondria and protect mitochondria against the oxidative damage induced by the xanthine oxidase/hypoxanthine pro-oxidant system. The observation that carvedilol acts as an inhibitor of mitochondrial complex-I is also of importance, since this mitochondrial system was proposed as cause of the **cardiotoxicity** associated with the antineoplasic drug **doxorubicin**. This review points out the major findings concerning the positive impact of carvedilol on mitochondrial function and its use in the treatment of myocardial diseases where oxidative stress is known to be involved. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L5 ANSWER 31 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 85001541 EMBASE
DOCUMENT NUMBER: 1985001541
TITLE: Drug-induced cardionecrosis.
AUTHOR: Godfraind T.
CORPORATE SOURCE: Laboratoire de Pharmacodynamie Generale et de Pharmacologie, Universite Catholique de Louvain, U.C.L. 7350, 1200 Bruxelles, Belgium
SOURCE: Archives of Toxicology, (1984) Vol. 55, No. SUPPL. 7, pp. 1-15. .
CODEN: ARTODN
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
052 Toxicology
030 Pharmacology
049 Forensic Science Abstracts
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB **Cardiotoxicity** may be defined as a drug action producing abnormalities in cardiac function, such as transitory disturbances or rhythm, conduction or contractility. Clearance of the drug is followed by recovery of the initial function. Cardionecrosis is the irreversible consequence of **cardiotoxicity**. Its appearance depends not only upon the toxicological potency of a given compound but may also depend upon the pathophysiological state of the heart. Therefore, two main categories may be recognized considering the influence of this state. Drugs may act on the processes controlling cellular structure such as protein biosynthesis in the case of antibiotics of the anthracycline group. Drugs may act at the level of metabolic regulation through a membranal or an intracellular action; in this case, the functional state of the heart plays a major role. This is mainly observed with sympathomimetics and with drugs interacting with the function of catecholamines. The **cardiotoxicity** observed in such conditions mimics the action of anoxia or of ischemia. The main determinant of the cardiac lesion is probably the disturbance of cellular calcium metabolism. This situation may be prevented (or treated) by the use of calcium entry blockers (calcium antagonists). A great part of this report will deal with the second group of drugs, because of their potential importance as a chemical hazard for the population and because of a possible preventive protection by calcium entry blockers (calcium antagonists).

L5 ANSWER 32 OF 55 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1984:316515 BIOSIS
DOCUMENT NUMBER: PREV198478052995; BA78:52995
TITLE: EFFECTS OF **ADRIAMYCIN** ON CALCIUM CONCENTRATION AND MORPHOLOGY OF MOUSE SALIVARY GLANDS.
AUTHOR(S): JIRAKULSOMCHOK D [Reprint author]; YU J-H; SHEETZ J H; SCHNEYER C A

CORPORATE SOURCE: DEP PHYSIOL BIOPHYSICS, UNIV ALABAMA BIRMINGHAM, UNIVERSITY STATION, BIRMINGHAM, ALA 35294, USA
SOURCE: Journal of Oral Pathology, (1983) Vol. 12, No. 6, pp. 491-501.
CODEN: JOPHBO. ISSN: 0300-9777.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB A large single dose (15 mg/kg body wt, i.p) of the antitumor agent **adriamycin** (ADR) caused a marked increase in Ca concentration of the submaxillary gland of female mice and a smaller increase in the parotid gland within 2 days of injection. A small dose (2.5 mg/kg body wt) had no effect. The histological appearance of the glands was also changed and included an increase in size of granules and acinar cells of the submaxillary glands and a decrease in size of acinar cells of the parotid. At the EM level, there was evidence of mitochondrial alteration in the parotid, but not in the submaxillary, glands. Rough endoplasmic reticulum (RER) was markedly disorganized in the parotid, and abnormal whorls of RER were evident. Submaxillary glands showed no change in RER. Water content of either gland was unchanged from that of controls. Heart ventricles, unexpectedly, showed no change in Ca concentration from that of control tissues at 3 h, 1, 2 or 4 days after ADR administration. The [Ca] changes induced by ADR in the submaxillary glands are not mediated via β-adrenoceptor activation since **propranolol** did not alter the ADR-induced changes. The marked difference in response of the glands (and heart) to ADR suggests that the mechanisms involved in Ca homeostatis in these organs are very different. [ADR is **cardiotoxic** and the mechanism of action is believed to involve Ca metabolism.].

L5 ANSWER 33 OF 55 EMBASE
ACCESSION NUMBER: 1999343955 EMBASE
TITLE: Cardioprotection.
AUTHOR: Levitt G.
CORPORATE SOURCE: Dr. G. Levitt, Department of Haematology/Oncology, Great Ormond Str. Hosp. for Children, NHS Trust, London WC1N 3JH, United Kingdom. gill.levitt@gosh-trnthames.nhs.uk
SOURCE: British Journal of Haematology, (1999) Vol. 106, No. 4, pp. 860-869. .
Refs: 100
ISSN: 0007-1048 CODEN: BJHEAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Oct 1999
Last Updated on STN: 21 Oct 1999
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 34 OF 55 MEDLINE on STN
ACCESSION NUMBER: 81186692 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7226457
TITLE: Direct and noninvasive evaluation of the cardiovascular response to isometric exercise.
AUTHOR: Perez-Gonzales J F; Schiller N B; Parmley W W
SOURCE: Circulation research, (1981 Jun) Vol. 48, No. 6 Pt 2, pp. I138-48.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198107
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 20 Jul 1981

AB One method for testing cardiac reserve is to increase arterial pressure by

isometric handgrip exercise (IHE) which increases the afterload against which the left ventricle must eject blood. In previous invasive studies in patients with cardiac disease, decreased ventricular reserve during IHE was manifest by a marked rise in LVEDP and a fall in cardiac output and stroke work index. To avoid the limitations of invasive techniques, we used M-mode echocardiography and other noninvasive measurements to evaluate the response to IHE in 11 normals and four patients with varying degrees of **adriamycin cardiotoxicity**. The normal response to IHE was manifest by an increase in heart rate (38%), arterial pressure (40%), cardiac output %53%), left ventricular end-diastolic diameter (12%), and endsystolic diameter (6%). There was no essential change in systemic vascular resistance, fractional shortening, or ejection fraction. In five normal subjects, 2 hours after 80 mg of oral **propranolol**, the response to IHE was altered as follows. Although the rise in arterial pressure was the same, the heart rate increase was blunted, and there was no significant rise in cardiac output. In the **adriamycin**-treated group the resting heart rate was higher, but the blood pressure response to IHE was the same. Compared to the normals, the **adriamycin** group had a fall in VCF and a rise in fractional shortening and ejection fraction, together with a rise in end-systolic diameter. Although further studies must be performed, noninvasive characterization of IHE may be helpful in evaluating ventricular reserve.

L5 ANSWER 35 OF 55 EMBASE

ACCESSION NUMBER: 93210321 EMBASE
DOCUMENT NUMBER: 1993210321
TITLE: In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle.
AUTHOR: Mosseri M.; Fingert H.J.; Varticovski L.; Chokshi S.; Isner J.M.
CORPORATE SOURCE: St. Elizabeth's Hospital, 736 Cambridge St,Boston, MA 02135, United States
SOURCE: Cancer Research, (1993) Vol. 53, No. 13, pp. 3028-3033. .
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Aug 1993
Last Updated on STN: 15 Aug 1993
AB 5-Fluorouracil (5-FU) is a commonly employed chemotherapeutic agent. Among the various toxicities associated with 5-FU, cardiovascular toxicity, consisting principally of acute myocardial ischemia and/or myocardial infarction, has been reported in up to 8.5% of patients treated with this drug. While 5-FU-induced coronary vasospasm has been considered as a potential basis for such clinical toxicity, this hypothesis remains unsubstantiated by laboratory investigation. Accordingly, the present study was designed to investigate the hypothesis that 5-FU induces reversible vasoconstriction of vascular smooth muscle and to study the cellular mechanisms of such vasomotor alterations. To investigate the effects of 5-FU on the vasoreactivity of vascular smooth muscle, 479 exposures were performed in 105 rings of aorta freshly isolated from 23 New Zealand white rabbits. Vasoconstriction was documented in 20 of 86 (23%) rings exposed to 5-FU at 7 x 10-5 M, 45 of 83 (54%) rings exposed to 5-FU at 7 x 10-4 M, and 41 of 49 (84%) rings exposed to 5-FU at 7 x 10-3 M. In each case, 5-FU-induced vasoconstriction was endothelium independent. Pretreatment of rings with 10- 9 M staurosporine, a protein kinase C (PK-C) inhibitor, reduced 5-FU- induced vasoconstriction from 25.0 ± 6.5 to 2.5 ± 1.7 mg; staurosporine at a concentration of 10-8 M abolished 5-FU-induced vasoconstriction. Pretreatment of rings with 10-7 M phorbol-12,13-dibutyrate, an activator of PK-C, increased the magnitude of 5-FU-induced vasoconstriction 23-fold, from 49.7 ± 11.1 mg before to 1163.6 ± 276.4 mg after phorbol-12,13-dibutyrate (P = 0.0002). Neomycin, an inhibitor of phosphoinositide turnover, did not

alter the magnitude of 5-FU-induced vasoconstriction. Membrane receptor blockers, including the α-adrenergic receptor blocker phentolamine, the β- adrenergic receptor blocker **propranolol**, the H1 receptor inhibitor diphenhydramine, the H2 receptor inhibitor cimetidine, the Ca2+ channel blockers verapamil and diltiazem, and the cyclooxygenase inhibitor indomethacin all failed to alter the magnitude of 5-FU-induced vasoconstriction. Furthermore, the 5-FU-related compounds uracil and floxuridine did not produce vasoconstriction. Finally, 5-FU-induced vasoconstriction was abolished by nitroglycerin. These results indicate that (a) 5-FU causes direct, endothelium-independent vasoconstriction of vascular smooth muscle in vitro, (b) this vasomotor response involves activation of PK-C, and (c) this response is independent of vasoactive cell membrane receptors, phosphoinositide turnover, or activation of the cyclooxygenase pathway. These findings suggest that the cardiovascular toxicity of 5-FU is due to PK-C-mediated vasoconstriction of vascular smooth muscle.

L5 ANSWER 36 OF 55 EMBASE

ACCESSION NUMBER: 85070472 EMBASE
DOCUMENT NUMBER: 1985070472
TITLE: Dynamic left ventricular outflow obstruction and myocardial infarction following **doxorubicin** administration in a woman affected by unsuspected hypertrophic cardiomyopathy.
AUTHOR: Mancuso L.; Marchi S.; Canonico A.; et al.
CORPORATE SOURCE: Divisione di Cardiologia, Ospedale V. Cervello, Palermo, Italy
SOURCE: Cancer Treatment Reports, (1985) Vol. 69, No. 2, pp. 241-244. .
CODEN: CTRRDO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 37 OF 55 EMBASE

ACCESSION NUMBER: 81041800 EMBASE
DOCUMENT NUMBER: 1981041800
TITLE: Depression of left ventricular function after a single dose of **adriamycin** in dogs.
AUTHOR: Ditchey R.V.; LeWinter M.M.; Pavelec R.; et al.
CORPORATE SOURCE: VA Med. Cent., San Diego, Calif., United States
SOURCE: Circulation, (1980) Vol. 62, No. 4 II, pp. No.1151. .
CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L5 ANSWER 38 OF 55 EMBASE

ACCESSION NUMBER: 2004400303 EMBASE
TITLE: Combretastatin A4 phosphate: Background and current clinical status.
AUTHOR: Young S.L.; Chaplin D.J.
CORPORATE SOURCE: S.L. Young, OXiGENE Inc., 230 Third Avenue, Waltham, MA 02451, United States. syoung@oxigene.com
SOURCE: Expert Opinion on Investigational Drugs, (2004) Vol. 13, No. 9, pp. 1171-1182. .
Refs: 59

ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 2004
Last Updated on STN: 7 Oct 2004

AB Combretastatin A4 phosphate (CA4P) represents the lead compound in a group of novel tubulin depolymerising agents being developed as vascular targeting agents (VTAs). VTAs are drugs that induce rapid and selective vascular dysfunction in tumours. CA4P is a water-soluble prodrug of the cis-stilbene CA4 originally isolated from the tree Combretum caffrum. Preclinical studies have shown that CA4P induces blood flow reductions and subsequent tumour cell death in a variety of preclinical models. Moreover, this activity has been linked to its ability to rapidly alter the morphology of immature endothelial cells by disrupting their tubulin cytoskeleton. Phase I clinical trials have established a maximum tolerated dose in the range 60 - 68 mg/m(2) and in addition have established that significant changes to tumour perfusion can be achieved across a wide range of doses. The dose-limiting toxicities include tumour pain, ataxia and cardiovascular changes. The maximum tolerated dose was independent of schedule, indicating the absence of cumulative toxicity. Although unexpected from preclinical studies, some evidence of clinical response was seen using CA4P as a single modality. Based on the Phase I data, combination studies of CA4P with established therapies are in progress and should determine whether the exciting preclinical data obtained when VTAs are used in combination with cytotoxic chemotherapy, radiation, radioimmunotherapy and even antiangiogenic agents, can be translated into man. 2004 .COPYRGT. Ashley Publications Ltd.

L5 ANSWER 39 OF 55 EMBASE
ACCESSION NUMBER: 93227833 EMBASE
DOCUMENT NUMBER: 1993227833
TITLE: Stereoisomers in clinical oncology: Why it is important to know what the right and left hands are doing.
AUTHOR: Wainer I.W.
CORPORATE SOURCE: Montreal General Hospital, 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada
SOURCE: Annals of Oncology, (1993) Vol. 4, No. SUPPL. 2, pp. S7-S13. .
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 1993
Last Updated on STN: 12 Sep 1993

AB Background: In the past few years it has become clear that the individual stereoisomers, especially the enantiomers, of a biologically active chiral molecule may differ in potency, pharmacological action, metabolism, toxicity, plasma disposition and urine excretion kinetics. The situation exists in all classes of therapeutically active agents including chiral agents used in clinical oncology. Chiral anticancer agents which exist as a pair of enantiomers are commonly administered as racemic (50:50) mixtures of the two isomers. The possibility exists that only one of the enantiomers possesses the desired pharmacological activity while the other is responsible for part or all of the observed toxicity. The toxicity due to the nonefficacious isomer may be the difference between a clinically useful anticancer drug and one which is too toxic to use. Results: The chiral compounds used in standard and experimental cancer chemotherapy

include leucovorin, ifosfamide and verapamil. Only one stereoisomer of leucovorin, (6S)-leucovorin is active and data suggests that the administration of just the single isomer may enhance the activity of the agent as well as improve therapeutic monitoring. Both enantiomers of verapamil, (R)-verapamil and (S)-verapamil, are active in reversing **adriamycin** resistance in some tumor lines. The standard clinical formulation of verapamil is a mixture of the two isomers and cannot be used in clinical treatment of resistant disease due to the **cardiotoxicity** of the (S)-isomer. (S)-verapamil is the active calcium channel blocking agent while (R)-verapamil has no effect in this area. Thus, an effective anticancer drug would be (R)-verapamil. Data also exists which suggests that the use of a single isomer of ifosfamide may reduce dose limiting CNS toxicity. Conclusion: The existence of stereoisomeric forms of a chemical has been a recognized fact for almost 150 years. However, the clinical consequences of symmetry and asymmetry are only just beginning to be considered. Within the three-dimensional structures of the human body lie tremendous potentials for differential drug actions and, perhaps, new keys to the treatment of cancer and other diseases. The next few years should see the end to the two- dimensional clinical pharmacology we are accustomed to and the growth of stereochemical clinical pharmacology; where we always know what the right and left hands are doing.

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ACCESSION NUMBER: 83087141 EMBASE
DOCUMENT NUMBER: 1983087141
TITLE: Cardiomyopathy: How far have we come in 25 years, how far yet to go?.
AUTHOR: Shabetai R.
CORPORATE SOURCE: Dep. Cardiol., Veterans Adm. Med. Cent., San Diego, CA 92161, United States
SOURCE: Journal of the American College of Cardiology, (1983) Vol. 1, No. 1, pp. 252-263. .
CODEN: JACCDI
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB Twenty-five years ago clinical investigators began to appreciate that cardiomyopathy is an important and reasonably common form of heart disease. Since than several functional classifications have been proposed, the specific myocardial diseases have been classified and chronic ischemic ventricular failure has been described. The boundary separating myocarditis from dilated cardiomyopathy remains hazy and, despite intensive research, the causes of dilated cardiomyopathy remain obscure. In particular, we still do not understand the role that may be played by viral infection and alcohol. Myocardial biopsy has proved useful in patients with specific myocardial disorders, heart transplant recipients and patients receiving **Adriamycin**, but is disappointing in patients with dilated cardiomyopathy. It has become increasingly evident that exercise capacity does not correlate with ventricular function, being highly dependent on peripheral factors. Measurements of oxygen consumption during exercise promise to be useful in assessing treatment of dilated cardiomyopathy. True restrictive cardiomyopathy is uncommon, and the term should be reserved for cardiomyopathies that meet strict criteria. A restrictive component to filling is common to many cardiac disorders, including some cases of cardiac amyloidosis. The concept of hypertrophic cardiomyopathy has evolved rapidly over the past 25 years, and continues to evolve. The importance of arrhythmia as a cause of sudden death is becoming increasingly clear. The place of calcium channel blocking agents in the treatment of hypertrophic cardiomyopathy will probably emerge soon. Amiodarone is finding an increasing role in the treatment of dilated and

hypertrophic cardiomyopathy. Surgical treatment is still required for some patients despite unanswered questions on how it works.

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ACCESSION NUMBER: 78125243 EMBASE
DOCUMENT NUMBER: 1978125243
TITLE: Drug induced cardiovascular diseases.
AUTHOR: Deglin S.M.; Deglin J.M.; Chung E.K.
CORPORATE SOURCE: Dept. Med., Div. Cardiol., West Virginia Univ. Sch. Med., Morgantown, W.Va., United States
SOURCE: Drugs, (1977) Vol. 14, No. 1, pp. 29-40. .
CODEN: DRUGAY
COUNTRY: Australia
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
030 Pharmacology
037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
040 Drug Dependence, Alcohol Abuse and Alcoholism
LANGUAGE: English

AB A wide variety of drugs may be associated with serious cardiovascular toxicity. Toxicity due to drugs primarily used for treating cardiac disorders is the most extensively documented, especially the arrhythmias due to digitalis glycosides. Various arrhythmias are also caused by toxic levels of many antiarrhythmic agents including quinidine, procainamide and phenytoin. Myocardial depression and heart failure are serious side-effects of β-adrenoceptor blocking agents and myocardial ischaemia due to sympathomimetic amines may result from both direct and indirect mechanisms. The many toxic reactions in the cardiovascular system due to non-cardiac drugs are less widely known and for the most part less clearly understood. Many remain controversial at the current time; for example, the diathesis toward thromboembolism in women taking oral contraceptives. Potential cardiac toxicity due to drugs used in the rapidly expanding sphere of antineoplastic chemotherapy is exemplified by the cardiomyopathy-like toxicities of **doxorubicin** and daunorubicin. Many of the psychotherapeutic drugs including phenothiazine antipsychotics and tricyclic antidepressants have arrhythmogenic potential.

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ACCESSION NUMBER: 95229729 EMBASE
DOCUMENT NUMBER: 1995229729
TITLE: Nuclear cardiology, current applications in clinical practice.
AUTHOR: Niemeyer M.G.; Van der Wall E.E.; Kuijper A.F.M.; Cleophas A.T.; Pauwels E.K.J.
CORPORATE SOURCE: DDRNM, Building 1, University Hospital, Rijnsburgerweg 10,2333 AA Leiden, Netherlands
SOURCE: Angiology, (1995) Vol. 46, No. 7, pp. 591-602. .
ISSN: 0003-3197 CODEN: ANGIAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
023 Nuclear Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 1995
Last Updated on STN: 27 Aug 1995

AB The clinical applications of nuclear cardiology have rapidly expanded since the introduction of suitable imaging cameras and readily applicable isotopes. The currently available methods can provide useful data on estimates of ventricular function and detection of myocardial ischemia for adequate patient management. Two standard procedures are routinely used: (1) myocardial perfusion scintigraphy, eg, with thallium 201; and (2) radionuclide angiocardiography by using technetium 99m-labeled red blood

cells. Myocardial perfusion scintigraphy provides information on regional viability and estimates regional myocardial perfusion by measuring regional tracer activity. Thallium 201 is the agent used for noninvasive assessment of myocardial perfusion and for improving the results of exercise electrocardiography. Alternative tests, such as pharmacologic stress testing with dipyridamole, have been proposed as a reliable substitute for exercise testing. Additional quantitative analysis and computed tomography have increased the sensitivity and specificity of thallium scintigraphy. Radionuclide angiography techniques are used for the noninvasive evaluation of cardiac function, right and left ventricular function, and wall motion abnormalities. As in perfusion scintigraphy, radionuclide angiography has proven its value for the detection of coronary artery disease (CAD). Abnormal regional wall motion abnormalities are specific for CAD.

L5 ANSWER 43 OF 55 EMBASE

ACCESSION NUMBER: 92305769 EMBASE
DOCUMENT NUMBER: 1992305769
TITLE: P-Glycoprotein-mediated multidrug resistance and cytotoxic effector cells.
AUTHOR: Savas B.; Cole S.P.C.; Akoglu T.F.; Pross H.F.
CORPORATE SOURCE: Dept. of Microbiology and Immunology, Queen's University,Kingston, Ont. K7L 3N6, Canada
SOURCE: Natural Immunity, (1992) Vol. 11, No. 4, pp. 177-192. .
ISSN: 1018-8916 CODEN: NAIMEL
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 1992
Last Updated on STN: 8 Nov 1992

AB Multidrug resistance (MDR) is one of the major obstacles to successful cancer chemotherapy. MDR is a complex and multifactorial phenomenon. One important and common mechanism used by cancer cells as a defense against cytotoxic drugs is a 170-kd plasma membrane glycoprotein, P-glycoprotein (P-gp). P-gp confers resistance by actively pumping cytotoxic drugs out of cancer cells. Paradoxically, P-gp overexpression on tumor cells is frequently associated with enhanced susceptibility to lymphokine-activated killer cell activity. This enhanced susceptibility is not observed with P-gp- MDR cells, nor is susceptibility to natural killer cells increased. The physiologic, evolutionary and immunologic concepts with regard to the P-gp and the possible intervention of the function of the P-gp in cancer therapy are reviewed.

L5 ANSWER 44 OF 55 EMBASE

ACCESSION NUMBER: 2006203458 EMBASE
TITLE: Heart failure therapy in children.
AUTHOR: Odland H.H.; Thaulow E.M.D.
CORPORATE SOURCE: Dr. E.M.D. Thaulow, Department of Pediatrics, University Hospital Oslo, Rikshospitalet, Oslo, Norway. erik.thaulow@medisin.uio.no
SOURCE: Expert Review of Cardiovascular Therapy, (2006) Vol. 4, No. 1, pp. 33-40. .
Refs: 61
ISSN: 1477-9072 E-ISSN: 1744-8344 CODEN: ERCTAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
017 Public Health, Social Medicine and Epidemiology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 2006
Last Updated on STN: 18 May 2006

AB The most common reason for heart failure in children is volume overload secondary to a left-to-right shunt. Therefore, an accurate diagnosis with identification of possible surgical or interventional reactions should be the first priority. Medical therapy is mainly based on diuretics, angiotensin-converting enzyme inhibitors, cardiac glycosides and β-blockers. There are few prospective trials in pediatric cardiology, but the available data reach a similar conclusion to that of adults with heart failure. Diuretics are an important tool in patients with fluid retention, and angiotensin-converting enzyme inhibitors are helpful in patients with volume overload of the ventricles. Cardiac glycosides are still in use, but there is a trend toward primary use of diuretics. Angiotensin-converting enzyme inhibitors and β-blockers have been used successfully in the treatment of heart failure in children, but there are limited data on its efficacy. .COPYRGT. 2006 Future Drugs Ltd.

L5 ANSWER 45 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 93347268 EMBASE
DOCUMENT NUMBER: 1993347268
TITLE: Stereoselective separations of chiral anticancer drugs and their application to pharmacodynamic and pharmacokinetic studies.
AUTHOR: Wainer I.W.; Granvil C.P.
CORPORATE SOURCE: Department of Oncology, McGill University,Montreal, Que. H3G 1Y6, Canada
SOURCE: Therapeutic Drug Monitoring, (1993) Vol. 15, No. 6, pp. 570-575. .
ISSN: 0163-4356 CODEN: TDMODV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Dec 1993
Last Updated on STN: 26 Dec 1993

AB In the past few years, it has become clear that individual stereoisomers-especially the enantiomers-of a biologically active chiral molecule may differ in potency, pharmacological action, metabolism, toxicity, plasma disposition, and urine excretion kinetics. This situation exists in all classes of therapeutically active agents including chiral anticancer agents. The chiral compounds used in standard and experimental cancer chemotherapy include leucovorin (LV), ifosfamide (IFF), buthionine sulfoximine (BSO), and verapamil (VER). Analytical methods for stereoselective separation of each of these compounds have been developed and applied to pharmacokinetic and pharmacodynamic studies. Pharmacological differences have been found between stereoisomers of all of these compounds and it is evident that the clinical effectiveness of these agents would be enhanced by the administration of only a single isomer.

L5 ANSWER 46 OF 55 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005327526 EMBASE
TITLE: Drug-associated mitochondrial toxicity and its detection.
AUTHOR: Amacher D.E.
CORPORATE SOURCE: D.E. Amacher, Worldwide Safety Sciences, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, United States. david.e.amacher@pfizer.com
SOURCE: Current Medicinal Chemistry, (2005) Vol. 12, No. 16, pp. 1829-1839. .
Refs: 143
ISSN: 0929-8673 CODEN: CMCHE7

COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 2005
Last Updated on STN: 5 Aug 2005

AB Mitochondrial dysfunction is a fundamental mechanism in the pathogenesis of several significant toxicities in mammals, especially those associated with the liver, skeletal and cardiac muscle, and the central nervous system. These changes can also occur as part of the natural aging process and have been linked to cellular mechanisms in several human disease states including Parkinson's and Alzheimer's, as well as ischemic perfusion injury and the effects of hyperglycemia in diabetes mellitus. Our knowledge of the effects of xenobiotics on mitochondrial function has expanded to the point that chemical structure and properties can guide the pharmaceutical scientist in anticipating mitochondrial toxicity. Recognition that maintenance of the mitochondrial membrane potential is essential for normal mitochondrial function has resulted in the development of predictive cell-based or isolated mitochondrial assay systems for detecting these effects with new chemical entities. The homeostatic role of some uncoupling proteins, differences in mitochondrial sensitivity to toxicity, and the pivotal role of mitochondrial permeability transition (MPT) as the determinant of apoptotic cell death are factors that underlie the adverse effects of some drugs in mammalian systems. In order to preserve mitochondrial integrity in potential target organs during therapeutic regimens, a basic understanding of mitochondrial function and its monitoring in the drug development program are essential. Toward this end, this review focuses on two topics, (1) the specific effects of xenobiotics on mitochondrial structure and function and (2) a summarization of current methods for quantifying these changes in a preclinical toxicology laboratory. .COPYRGT. 2005 Bentham Science Publishers Ltd.

ACCESSION NUMBER: 2005074241 EMBASE
TITLE: Highlights of the 2004 Scientific Sessions of the Heart Failure Society of America, Toronto, Canada, September 12 to 15, 2004.
AUTHOR: Liu P.; Konstam M.A.; Force T.
CORPORATE SOURCE: Dr. T. Force, Tufts-New England Medical Center, Molec. Cardiology Research Institute, Box 8486, 750 Washington Street, Boston, MA 02111, Canada. TForce@tufts-nemc.org
SOURCE: Journal of the American College of Cardiology, (15 Feb 2005) Vol. 45, No. 4, pp. 617-625. .
ISSN: 0735-1097 CODEN: JACCDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2005
Last Updated on STN: 10 Mar 2005

AB The annual scientific meeting of the Heart Failure Society of American (HFSA) brings together cardiologists, surgeons, nurses, and allied health care workers who are interested in improving the diagnosis, treatment, quality of life, and survival of patients affected by heart failure. The meeting integrates the best of basic advances with clinical trials and outcomes observations in a single seamless forum. The meeting in Toronto, Canada, attracted close to 3,000 attendees. .COPYRGT. 2005 by the American College of Cardiology Foundation.

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ACCESSION NUMBER: 2001192495 EMBASE
TITLE: Clinical pharmacokinetics of docetaxel: A review.
AUTHOR: Schriever U.; Nagel J.D.; Bode U.
CORPORATE SOURCE: U. Bode, Dept. of Pediatric Oncol./Hematology, University of Bonn, Adenauerallee 119, D-53113 Bonn, Germany
SOURCE: International Journal of Pediatric Hematology/Oncology, (2000) Vol. 7, No. 2, pp. 127-138. .
Refs: 56
ISSN: 1070-2903 CODEN: IPHOE4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jun 2001
Last Updated on STN: 14 Jun 2001

AB Docetaxel is a member of the taxoid class of antineoplastic agents which is now undergoing clinical phase II and III studies in the USA, Europe, and Japan. The pharmacokinetic behavior of docetaxel in pediatric patients is almost unknown although it may soon play a major role in pediatric oncology. Since the pharmacokinetics in adults and children may be expected to be similar, the available data of adults may serve as valuable information in order to design clinical studies in pediatric patients. Thus, it was our intention to summarize the available pharmacokinetic data. Depending on the used schedule the decline of the plasma concentration-time curve was bi- or triphasic. The administered doses ranged from 20 mg/m(2) to 115 mg/m(2) given as 1- to 24-hour infusions. The maximum tolerated dose was in between 70 and 125 mg/m(2), the peak-concentration - generally achieved at the end of infusion - reached values of 0.6 to 4.33 μmol/1. Consistently, the volume of distribution was larger than the total amount of body water (11-310 I/m(2)). There was no diffusion to the CNS. The binding of docetaxel to plasma proteins is fast and nearly complete (up to 98% of the dose). The area under the curve ranged from 0.4 to 4.6 μg/ml.ovrhdot.h (1-hour infusion) and from 1.1 to 9.1 μg/ml.ovrhdot.h (24-hour infusion). After biotransformation by the CYP3A sub-family of the cytochrome P450 isoenzymes, Docetaxel is mainly excreted with the bile. 75% of the dose were found in the faeces within 48 hours after application, whereas the renal excretion accounted for less than 10%. Independent of the schedule the clearance ranged from 194 ml/m(2)/min to 995 ml/m(2)/min. The half-life of distribution was 3.0 to 7.6 min. In case of triphasic elimination the β-half-life was 36 to 63 min and the terminal half-life ranged between 1.0 to 11.9 hours (biphasic elimination) and 9.6 to 18.5 hours (triphasic elimination). Knowledge of the pharmacokinetics of docetaxel will help to design further investigations in children more efficiently and appropriately. Thus, it may be possible to reduce the number of blood samples (three samples per phase of the concentration-time curve should be sufficient). Furthermore, the concentration at the end of infusion may be useful to estimate the pharmacodynamic effects and possibly to predict the efficacy of treatment.

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ACCESSION NUMBER: 96193930 EMBASE
DOCUMENT NUMBER: 1996193930
TITLE: Cardiovascular diseases in women: An equal opportunity killer.
AUTHOR: Morgan N.A.; Colling C.L.; Fye C.L.
CORPORATE SOURCE: Department of Veterans Affairs, Cooperative Studies Program, Clin. Res. Pharmacy Coordin. Center,Albuquerque, NM, United States
SOURCE: Journal of the American Pharmaceutical Association, (1996)

L28 ANSWER 1 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 86027433 EMBASE
DOCUMENT NUMBER: 1986027433
TITLE: The beneficial effect of amrinone on acute **drug-induced heart failure** in the anaesthetised dog.
AUTHOR: Alousi A.A.; Canter J.M.; Fort D.J.
CORPORATE SOURCE: Department of Cardiovascular Pharmacology, Sterling-Winthrop Research Institute, Rensselaer, NY 12144, United States
SOURCE: Cardiovascular Research, (1985) Vol. 19, No. 8, pp. 483-494. .
CODEN: CVREAU
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB Amrinone, a positive inotropic-vasodilator agent, was administered to anaesthetised dogs in an attempt to reverse **heart failure** induced by drugs possessing negative inotropic properties. **Propranolol**, a β-adrenergic blocker; verapamil, a calcium slow-channel blocker procainamide, a type 1 antiarrhythmic agent; or sodium pentobarbital, a barbiturate; administered as a bolus injection and/or infusion, produced a sustained depression in canine cardiac function. Cardiac depression was characterised by a greater than 40% reduction in cardiac contractile force (CF) and maximum left ventricular pressure development (LV dp/dt(max)), a 30 to 50% reduction in cardiac output (CO) and concomitant increases in mean central venous or mean right atrial blood pressures (CVP, RAP, respectively). Amrinone, when administered intravenously as a bolus injection (1 or 3 mg·kg-1) plus an infusion (0.03 or 0.1 mg·kg-1·min-1) reversed the depression in cardiac function by increasing CF, CO and LV dp/dt(max) and decreasing preload CVP or RAP in all four **drug-induced** failure models. Due to the vasodilator properties of amrinone, afterload, total peripheral resistance (TPR), was reduced in verapamil and procainamide failures as well as in **propranolol** failure, the only model where TPR increases. In another model of **heart failure**, in which ouabain-induced **arrhythmias** preceded procainamide toxicity, amrinone was also an effective cardiotonic agent. Ouabain's inotropic effect was studied in **propranolol**-induced **heart failure**. Although an increase in LV dp/dt(max) and a decrease in CVP were noted, ouabain (40 μg·kg-1 iv) increased TPR and had litle effect on the depression in CF and CO. **Drug-induced** models of **heart failure** were useful pharmacological tools for evaluating the cardiotonic agent's ability to overcome severe cardiac depression. In **propranolol**-, verapamil-, procainamide-, and pentobarbital-induced cardiac toxicity, amrinone could be of therapeutic value.

L28 ANSWER 2 OF 13 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 78382465 EMBASE
DOCUMENT NUMBER: 1978382465
TITLE: Subclinical adriamycin **cardiotoxicity**: detection by timing the arterial sounds.
AUTHOR: Greco F.A.
CORPORATE SOURCE: Dept. Med., Vanderbilt Univ. Med. Cent., Nashville, Tenn., United States
SOURCE: Cancer Treatment Reports, (1978) Vol. 62, No. 6, pp. 901-905. .
CODEN: CTRRDO
COUNTRY: United States
DOCUMENT TYPE: Journal

FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
025 Hematology
LANGUAGE: English

AB 'Sphygmo-Recording', a noninvasive method for timing the arterial pulse wave contour, provides a measurement (QK(d) interval) which reflects changes in myocardial contractility and stroke output. The QK(d) interval, ie, the time between the onset of the QRS complex (Q) and the onset of the Korotkoff sounds (K) at the brachial artery at diastolic pressure (d), is the sum of the cardiac pre-ejection period and the pulse transmission time. Serial QK(d) intervals were done in patients receiving adriamycin (ADM) alone, in sequence with other **chemotherapy**, in combination **chemotherapy**, and in combination with radiotherapy. The QK(d) interval was significantly prolonged (>30 msec) within 1-3 weeks after ADM therapy alone or in combination therapy in >50% of patients after the first dose and subsequently. Although similar changes were seen in patients receiving ADM in combination with cyclophosphamide, vincristine, and mediastinal radiotherapy, these patients often showed repeated and sustained QK(d) elevations. The QK(d) interval returned to baseline in most patients 2-4 months after stopping ADM. Four of seven patients receiving >550 mg/m2 of ADM developed congestive **heart failure**. In three patients, the QK(d) interval failed to return to baseline values during ADM therapy 1-3 months prior to any other evidence of **heart failure**. In the fourth patient, ADM was stopped prior to **heart failure** after the QK(d) failed to return toward baseline levels; the QK(d) returned to normal for 4 months but abruptly increased in association with severe congestive **heart failure**. The QK(d) interval appears to reflect subclinical ADM **cardiotoxicity**. Although weekly serial QK(d) measurements may be useful in more accurately predicting clinical cardiomyopathy in patients receiving >550 mg/m2, it is not specific nor absolutely reliable.

L28 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:470872 CAPLUS
DOCUMENT NUMBER: 113:70872
TITLE: Isolated mouse atrium as a model to study anthracycline **cardiotoxicity**: the role of the β-adrenoceptor system and reactive oxygen species
AUTHOR(S): De Jong, J.; Schoofs, P. R.; Onderwater, R. C. A.; Van der Vijgh, W. J. F.; Pinedo, H. M.; Bast, A.
CORPORATE SOURCE: Dep. Oncol., Free Univ., Amsterdam, 1081 HV, Neth.
SOURCE: Research Communications in Chemical Pathology and Pharmacology (1990), 68(3), 275-89
CODEN: RCOCB8; ISSN: 0034-5164
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cancer **chemotherapy** with anthracyclines, of which doxorubicin (DX) is the main representative, is limited by cardiomyopathy developing in animals and patients after cumulative dosing. The toxicity is probably related to free radical formation by the anthracycline as well as its metabolites with concomitant O2- and OH generation resulting in lipid peroxidn. and subsequent membrane damage. Isolated mouse atrium was chosen as an in vitro model to investigate the individual contribution of each metabolite to **cardiotoxicity**, since the mouse lacks the DX-induced nephrotic syndrome seen for instance in rats and rabbits. To characterize the model, l-isoprenaline/dl-propanolol and metacholine/atropine were used to measure the β-adrenergic and the muscarinic responses of (spontaneously beating) right and (paced) left atrium. Dose response curves were highly reproducible: pD2,iso = 8.0 (left) and 8.5 (right); pD2,met = 6.7 (left) and 6.2 (right). **Propranolol** as well as atropine behaved as competitive antagonists, with pA2-values of 8.4/8.5 (l/r) and 9.1/9.1 (l/r), resp. These values corresponded to those obtained with other organ prepns. The effect of DX was tested in two ways: a) by measuring the direct inotropic

and chronotropic effect during 60 min of incubation with 10-100 μM DX in the organ bath, and b) by determining the remaining β-adrenergic response to l-isoprenaline after the incubation period. Both variables turned out to be equally affected. For paced left atria an IC50 (causing 50% depression of contractile force) of 35 μM was determined Right atria stopped beating at concns. above 50 μM, thus hampering IC50 determination The results indicate that anthracyclines exert an effect not related to receptor integrity, but directly to the functionality of heart muscle. The check whether radical stress can be involved in the observed neg. inotropic effect, incubations with xanthine/xanthine involved in the observed neg. inotropic effect, incubations with xanthine/xanthine oxidase (to produce reactive oxygen species) were performed. A pronounced neg. effect on mouse atrial contraction was indeed observed However, initially a pos. inotropic effect accompanied by an increased resting tension was seen. Thus, mouse atrium can be used as a model to compare anthracyclines and their metabolites with regard to their acute **cardiotoxic** effects.

L28 ANSWER 4 OF 13 EMBASE

ACCESSION NUMBER: 86153734 EMBASE
DOCUMENT NUMBER: 1986153734
TITLE: Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing.
AUTHOR: Poser R.F.; Podrid P.J.; Lombardi F.; Lown B.
CORPORATE SOURCE: Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, United States
SOURCE: American Heart Journal, (1985) Vol. 110, No. 1 I, pp. 9-16.
.
CODEN: AHJOA2
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB There is evidence that antiarrhythmic drugs can worsen ventricular **arrhythmias** in patients. In a previous study ventricular **arrhythmias** worsened 11% when noninvasive monitoring and exercise tests were performed to evaluate drug effect. How frequently this complication occurs when patients undergo electrophysiologic studies is not known. Electrophysiologic (EP) tests were carried out in 63 patients who had a history of malignant, sustained ventricular tachyarrhythmias. Monitoring and exercise tests showed low-frequency or nonreproducible ventricular **arrhythmia**. Criteria for definite **drug-induced** aggravation of **arrhythmia** included (1) conversion of nonsustained ventricular tachycardia to a sustained ventricular **arrhythmia** and (2) provocation of the end point with one extrastimulus when three were required during control. Aggravation was deemed possible when, as compared to a control group, the end point resulted with the use of one less extrastimulus and sustained tachycardia with a more rapid rate was provoked. A total of 216 single drug studies were performed (3.4/patient). In general, definite or possible aggravation occurred in 35 tests (16%). In 28 cases (12.9%) aggravation was categorized as definite, while in 7 cases (3.2%) the induced arrythmia was deemed as possibly related to the use of the antiarrhythmic drugs. Drug tests with multiple agents caused aggravation of **arrhythmia** in 19 patients (30%). Therefore, exacerbation of **arrhythmia** by antiarrhythmic drugs also occurs during electrophysiologic study. The incidence approximates that reported when monitoring and exercise tests are used for evaluating drug efficacy.

L28 ANSWER 5 OF 13 EMBASE

ACCESSION NUMBER: 87202836 EMBASE
DOCUMENT NUMBER: 1987202836

TITLE: [On the efficacy of trapidil and some trapidil derivatives on **drug induced** cardiac **arrhythmias** rat and guinea-pig].
UBER DIE WIRKSAMKEIT VON TRAPIDIL UND EINIGEN TRAPIDIL-DERIVATEN AUF SUBSTANZINDUZIERTE HERZARRHYTHMIEN AN RATTE UND MEERSCHWEINCHEN.
AUTHOR: Riedel A.; Schneider S.; Mest H.-J.
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie der Martin-Luther-Universitat Halle-Wittenberg, DDR-4020 Halle/Saale, Germany
SOURCE: Arzneimittel-Forschung/Drug Research, (1987) Vol. 37, No. 8, pp. 923-926. .
CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991

AB Trapidil and some selected derivatives of trapidil were investigated on ouabain induced arrhythmia in guinea-pigs and in aconitine induced arrhythmia in rats. In both models trapidil exerted a marked antiarrhythmic effect. Investigations on ouabain induced arrhythmia showed that three derivatives were more effective than trapidil concerning the threshold for premature ventricular beats and flutter. One derivative only was able to decrease the sensitivity for fibrillation in the same order of magnitude as trapidil. On aconitine induced arrhythmia all derivatives of trapidil were less effective in elevating the threshold of arrhythmia than trapidil itself, but three derivatives showed antiarrhythmic properties.

L28 ANSWER 6 OF 13 EMBASE
ACCESSION NUMBER: 85157871 EMBASE
DOCUMENT NUMBER: 1985157871
TITLE: Aggravation of ventricular **arrhythmia**. A **drug-induced** complication.
AUTHOR: Podrid P.J.
CORPORATE SOURCE: Cardiovascular Laboratories, Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, United States
SOURCE: Drugs, (1985) Vol. 29, No. SUPPL. 4, pp. 33-44. .
CODEN: DRUGAY
COUNTRY: Australia
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
006 Internal Medicine
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB Each antiarrhythmic agent can cause side effects, but most of these are easily recognised by the patient or physician. However, one potentially serious side effect common to all of these drugs is aggravation of ventricular arrhythmia. Often this is without symptoms and goes unrecognised by the patient. It occurs in 11 to 16% of drug tests depending upon the method of drug evaluation employed. There are no ECG changes which predict its occurrence and blood concentrations of drug are usually within a therapeutic range. There are no clinical patient features which are associated with this toxic reaction and it does not correlate with the presence or extent of underlying heart diesase, the nature of the presenting arrhythmia or the known electrophysiological properties of the antiarrhythmic drug. Careful evaluation of these drugs is therefore essential.

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ACCESSION NUMBER: 1998256452 EMBASE
TITLE: Anthracycline-induced **cardiotoxicity**.
AUTHOR: Shan K.; Lincoff A.M.; Young J.B.
CORPORATE SOURCE: Dr. A.M. Lincoff, Experimental Interventional Lab., Department of Cardiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States
SOURCE: Annals of Internal Medicine, (1996) Vol. 125, No. 1, pp. 47-58. .
Refs: 146
ISSN: 0003-4819 CODEN: AIMEAS
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Aug 1998
Last Updated on STN: 20 Aug 1998

AB Purpose: To review the current understanding of the clinical significance, detection, pathogenesis, and prevention of anthracycline- induced **cardiotoxicity**. Data Sources: A MEDLINE search of the English-language medical literature and a manual search of the bibliographies of relevant articles, including abstracts from national cardiology meetings. Study Selection: Pertinent clinical and experimental studies addressing the clinical relevance, pathogenesis, detection, and prevention of anthracycline **cardiotoxicity** were selected from peer-reviewed journals without judgments about study design. A total of 137 original studies and 9 other articles were chosen. Data Extraction: Data quality and validity were assessed by each author independently. Statistical analysis of combined data was inappropriate given the differences in patient selection, testing, and follow-up in the available studies. Data Synthesis: Anthracyline-induced **cardiotoxicity** limits effective cancer **chemotherapy** by causing early cardiomyopathy, and it can produce late-onset ventricular dysfunction years after treatment has ceased. Detection of subclinical anthracyline-induced cardiomyopathy through resting left ventricular ejection fraction or echocardiographic fractional shortening is suboptimal. Conventional doses of anthracycline often lead to permanent myocardial damage and reduced functional reserve. Underlying pathogenetic mechanisms may include free-radical-mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and the release of **cardiotoxic** cytokines. Dexrazoxane is the only cardioprotectant clinically approved for use against anthracyclines, and it was only recently introduced for selected patients with breast cancer who are receiving anthracycline therapy. Conclusions: A rapidly growing number of persons, including an alarming fraction of the 150 000 or more adults in the United States who have survived childhood cancer, will have substantial morbidity and mortality because of anthracycline-related cardiac disease. The development of effective protection against anthracycline-induced **cardiotoxicity** will probably have a significant effect on the overall survival of these patients.

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ACCESSION NUMBER: 86060487 EMBASE
DOCUMENT NUMBER: 1986060487
TITLE: Drug-induced torsade de pointes.
AUTHOR: Raehl C.L.; Patel A.K.; LeRoy M.
CORPORATE SOURCE: School of Pharmacy, University of Wisconsin, Madison, WI 53706, United States
SOURCE: Clinical Pharmacy, (1985) Vol. 4, No. 6, pp. 675-690. .
CODEN: CPHADV
COUNTRY: United States

DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB Three patients who developed torsade de pointes associated with antiarrhythmic or psychotropic drugs are described, and the electrocardiographic characteristics, clinical presentation, predisposing factors, and management of this form of ventricular tachycardia are reviewed. The first patient was a 56-year-old schizophrenic man receiving thioridazine hydrochloride, trifluoperazine hydrochloride, and benztropine mesylate who was admitted to a hospital after a syncopal episode. Subsequently, the patient experienced several episodes of ventricular tachycardia combined with multifocal premature ventricular contractions (PVCs) and torsade de pointes; the **arrhythmias** were attributed to antipsychotic therapy. The second patient was a 69-year-old man who experienced ventricular tachycardia that progressed to ventricular fibrillation 41 days after surgery. Quinidine sulfate probably induced the ventricular tachycardia, which was identified as torsade de pointes. The thrid patient was a 71-year-old man admitted to the hospital for treatment of refractory ventricular **arrhythmias**. Previous drug therapy with quinidine sulfate and procainamide hydrochloride had been associated with torsade de pointes. Despite unsuccessful treatment of ventricular ectopy, the patient was discharged on maintenance therapy with pindolol, topical nitrates, and phenytoin. No additional episodes of torsade de pointes have been observed. Torsade de pointes is characterized by polymorphous electrocardiographic appearance and delayed repolarization (prolonged QT interval). It may occur in association with a number of disease states and also as a complication of treatment with therapeutic doses of drugs that affect repolarization (quinidine, disopyramide, procainamide, and phenothiazines). Clinical outcomes range from asymptomatic, self-terminating **arrhythmias** to ventricular fibrillation resulting in cardiac arrest. The definitive emergency therapy for torsade de pointes is ovedrive pacing; cautious isoproterenol administration can also be used. Lidocaine and bretylium are often ineffective in treating this form of ventricular tachycardia. Potassium and magnesium repletion appear to be essential in abolishing **drug -induced** torsade de pointes. **Drug-induced** torsade de pointes is best prevented by avoiding agents known to induce **arrhythmias** in patients with a pre-existing prolonged QT interval. Periodic serum electrolyte assessment is warranted, and new drugs that prolong the QT interval should be considered potential causative agents of torsade de pointes.

L28 ANSWER 9 OF 13 EMBASE
ACCESSION NUMBER: 83037979 EMBASE
DOCUMENT NUMBER: 1983037979
TITLE: Toxic cardiomyopathy due to doxorubicin.
AUTHOR: Bristow M.R.
CORPORATE SOURCE: Stanford Univ., Stanford, CA, United States
SOURCE: Hospital Practice, (1982) Vol. 17, No. 12, pp. 101-111. .
CODEN: HOPRBW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
052 Toxicology
018 Cardiovascular Diseases and Cardiovascular Surgery
016 Cancer
030 Pharmacology
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB The use of doxorubicin poses a clinical dilemma: This effective antitumor agent is also high **cardiotoxic**. Thus, cardiac failure has been all too common in patients whose cancers have been controlled. A protocol

based on identification and monitoring of patients with certain risk factors permits **chemotherapy** with little cardiac morbidity and virtually no mortality from **drug-induced** congestive failure.

L28 ANSWER 10 OF 13 EMBASE

ACCESSION NUMBER: 78125243 EMBASE
DOCUMENT NUMBER: 1978125243
TITLE: Drug induced cardiovascular diseases.
AUTHOR: Deglin S.M.; Deglin J.M.; Chung E.K.
CORPORATE SOURCE: Dept. Med., Div. Cardiol., West Virginia Univ. Sch. Med., Morgantown, W.Va., United States
SOURCE: Drugs, (1977) Vol. 14, No. 1, pp. 29-40. .
CODEN: DRUGAY
COUNTRY: Australia
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
030 Pharmacology
037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
040 Drug Dependence, Alcohol Abuse and Alcoholism
LANGUAGE: English

AB A wide variety of drugs may be associated with serious cardiovascular toxicity. Toxicity due to drugs primarily used for treating cardiac disorders is the most extensively documented, especially the **arrhythmias** due to digitalis glycosides. Various **arrhythmias** are also caused by toxic levels of many antiarrhythmic agents including quinidine, procainamide and phenytoin. Myocardial depression and **heart failure** are serious side-effects of β-adrenoceptor blocking agents and myocardial ischaemia due to sympathomimetic amines may result from both direct and indirect mechanisms. The many toxic reactions in the cardiovascular system due to non-cardiac drugs are less widely known and for the most part less clearly understood. Many remain controversial at the current time; for example, the diathesis toward thromboembolism in women taking oral contraceptives. Potential cardiac toxicity due to drugs used in the rapidly expanding sphere of antineoplastic **chemotherapy** is exemplified by the cardiomyopathy-like toxicities of doxorubicin and daunorubicin. Many of the psychotherapeutic drugs including phenothiazine antipsychotics and tricyclic antidepressants have arrhythmogenic potential.

L28 ANSWER 11 OF 13 EMBASE

ACCESSION NUMBER: 87101419 EMBASE
DOCUMENT NUMBER: 1987101419
TITLE: Prevention of streptozotocin-induced alterations in the rat heart by 3-O-methyl glucose and insulin treatments.
AUTHOR: Ramanadham S.; Young J.; Tenner Jr. T.E.
CORPORATE SOURCE: The University of British Columbia, Vancouver, BC V6T 1W5, Canada
SOURCE: Journal of Cardiovascular Pharmacology, (1987) Vol. 9, No. 3, pp. 291-297. .
CODEN: JCPCDT
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
003 Endocrinology
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991

AB Streptozotocin-induced diabetes has previously been shown to alter the sensitivity and responsiveness of rat myocardial tissues to cardiotonic agonists. The objective of the present study was to determine if these alterations were due to the diabetogenic or possible direct **cardiotoxic** effects of streptozotocin. One month after streptozotocin treatment the following changes were observed in the rat:

decrease in body weight; elevation of blood glucose and glycosylated hemoglobin levels; decrease in spontaneously beating atrial rate; elevation in basal developed force of electrically driven right ventricle; and inotropic subsensitivity of right ventricle to isoproterenol, which was associated with decreased β-adrenoceptor density and supersensitivity to calcium. Pretreatment with the nonmetabolizable glucose analog 3-O-methyl glucose prevented these alterations. Chronic insulin replenishment also reversed the effects of streptozotocin, with the exception of complete normalization of elevations in blood glucose and basal developed force. Acute exposure to high glucose in the medium preserved the subsensitivity to isoproterenol but resulted in an elevated basal developed force in both control and streptozotocin groups. These observations indicate that myocardial alterations after streptozotocin treatment are not the result of direct **cardiotoxic** effects but rather a consequence of the **drug-induced** diabetic state. They also suggest that the increase in basal developed force might be related to elevated glucose concentrations.

L28 ANSWER 12 OF 13 EMBASE

ACCESSION NUMBER: 2001080315 EMBASE

TITLE: High-dose mitoxantrone + melphalan (MITO/L-PAM) as conditioning regimen supported by peripheral blood progenitor cell (PBPC) autograft in 113 lymphoma patients: High tolerability with reversible **cardiotoxicity**.

AUTHOR: Tarella C.; Zallio F.; Caracciolo D.; Cuttica A.; Corradini P.; Gavarotti P.; Ladetto M.; Podio V.; Sargiotto A.; Rossi G.; Gianni A.M.; Pileri A.

CORPORATE SOURCE: C. Tarella, Cattedra di Ematologia, Via Genova 3, 10126 Torino, Italy

SOURCE: Leukemia, (2001) Vol. 15, No. 2, pp. 256-263. .
Refs: 50
ISSN: 0887-6924 CODEN: LEUKED

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 2001
Last Updated on STN: 16 Mar 2001

AB Hematological and extrahematological toxicity of high-dose (hd) mitoxantrone (MITO) and melphalan (L-PAM) as conditioning regimen prior to peripheral blood progenitor cell (PBPC) autograft was evaluated in 113 lymphoma patients (87 at disease onset). Autograft was the final part of a hd-sequential (HDS) **chemotherapy** program, including a debulkying phase (1-2 APO ±2 DHAP courses) and then sequential administration of hd-cyclophosphamide, methotrexate (or Ara-C) and etoposide, at 10 to 30 day intervals. Autograft phase included: (1) hd-MITO, given at 60 mg/m(2) on day -5; (2) hd-L-PAM, given at 180 mg/m(2) on day -2; (3) PBPC autograft, with a median of 11 x 10(6) CD34(+)/kg, or 70 x 10(4) CFU-GM/kg, on day 0. A rapid hematological recovery was observed in most patients, with ANC >500/μL and Plt >20 000/μI values reached at a median of 11 and 10 days since autograft, respectively. The good hemopoietic reconstitution allowed the delivery of consolidation radiotherapy (RT) to bulky sites in 53 out of 57 candidate patients, within 1 to 3 months following autograft; five of these patients required back-up PBPC re-infusion due to severe post-RT pancytopenia. Few severe infectious complications were recorded. There was one single fatal event due to severe pancytopenia following whole abdomen RT. Cardiac toxicity was evaluated as left ventricular ejection fraction (LVEF), monitored by cardiac radionuclide scan. LVEF prior to and after autograft was significantly reduced (median values: 55% vs 46%) in 58 evaluated patients; however, a significant increase to a median value of 50% was observed in 45 patients evaluated at 1 to 3 years since autograft. At a median follow-up of 3.6 years, 92 patients are alive, with a 7-year overall survival projection and 6.7-year failure-free survival projection

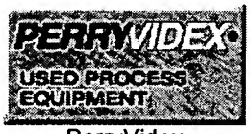
of 77% and 69%, respectively. We conclude that a conditioning regimen with hd-MITO/L-PAM fits well within the HDS program. It implies good tolerability and reversible **cardiotoxicity** and it may have contributed to the good long-term outcome observed in this series of patients.

L28 ANSWER 13 OF 13 EMBASE

ACCESSION NUMBER: 93227833 EMBASE
DOCUMENT NUMBER: 1993227833
TITLE: Stereoisomers in clinical oncology: Why it is important to know what the right and left hands are doing.
AUTHOR: Wainer I.W.
CORPORATE SOURCE: Montreal General Hospital, 1650 Cedar Avenue,Montreal, Que. H3G 1A4, Canada
SOURCE: Annals of Oncology, (1993) Vol. 4, No. SUPPL. 2, pp. S7-S13. .
ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 1993
Last Updated on STN: 12 Sep 1993

AB Background: In the past few years it has become clear that the individual stereoisomers, especially the enantiomers, of a biologically active chiral molecule may differ in potency, pharmacological action, metabolism, toxicity, plasma disposition and urine excretion kinetics. The situation exists in all classes of therapeutically active agents including chiral agents used in clinical oncology. Chiral anticancer agents which exist as a pair of enantiomers are commonly administered as racemic (50:50) mixtures of the two isomers. The possibility exists that only one of the enantiomers possesses the desired pharmacological activity while the other is responsible for part or all of the observed toxicity. The toxicity due to the nonefficacious isomer may be the difference between a clinically useful anticancer drug and one which is too toxic to use. Results: The chiral compounds used in standard and experimental cancer **chemotherapy** include leucovorin, ifosfamide and verapamil. Only one stereoisomer of leucovorin, (6S)-leucovorin is active and data suggests that the administration of just the single isomer may enhance the activity of the agent as well as improve therapeutic monitoring. Both enantiomers of verapamil, (R)-verapamil and (S)-verapamil, are active in reversing adriamycin resistance in some tumor lines. The standard clinical formulation of verapamil is a mixture of the two isomers and cannot be used in clinical treatment of resistant disease due to the **cardiotoxicity** of the (S)-isomer. (S)-verapamil is the active calcium channel blocking agent while (R)-verapamil has no effect in this area. Thus, an effective anticancer drug would be (R)-verapamil. Data also exists which suggests that the use of a single isomer of ifosfamide may reduce dose limiting CNS toxicity. Conclusion: The existence of stereoisomeric forms of a chemical has been a recognized fact for almost 150 years. However, the clinical consequences of symmetry and asymmetry are only just beginning to be considered. Within the three-dimensional structures of the human body lie tremendous potentials for differential drug actions and, perhaps, new keys to the treatment of cancer and other diseases. The next few years should see the end to the two- dimensional clinical pharmacology we are accustomed to and the growth of stereochemical clinical pharmacology; where we always know what the right and left hands are doing.

=>



Synonyms: 525-66-6, C07407, Propranolol, Propranolol, 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, beta-Propranolol, Obsidan, Proprasylyt, Reducor, AY 64043, Dociton, ICI 45520, Inderal, 1-Isopropylamino-3-(1-naphthyloxy)-2-propanol, NSC-91523, Propanalol, Propanolol, Propranalol, Reducor line, etalong, Avlocardyl, Euprovasin, NISTC525666, propranolol, 91523, 318-98-9, 1500514, P128, 624, 155333, CHEMBANK351, 1-((1-Methylethyl)amino)-3-(1-naphthalenyloxy)-2-propanol, 1-Isopropylamino-3-(1-naphthyloxy)-2-propanol, 2-Propanol, 1-((1-methylethyl)amino)-3-(1-naphthalenyloxy)-, 2-Propanol, 1-((1-methylethyl)amino)-3-(1-naphthalenyloxy)- (9CI), 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, 525-66-6, Betalong, CCRIS 3082, Corpendol, EINECS 208-378-0, Euprovasin, Inderal, PROPRANOLOL, Propanix, Propanolol, Propanolol [INN-Spanish], Propranololo [DCIT], Propranololum [INN-Latin], Proprasylyt, Reducor, Sawatal, Sumial, beta-Propranolol, 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, (R)-, 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, (+)-, Dexpropranolol, Dextropropranolol, (+)-Propranolol, d-Propranolol, d-(+)-Propranolol, R-(+)-Propranolol, (R)-Propranolol, 2R-Propranolol, (+)-1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol, 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol, 5051-22-9, Propranolol, 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, beta-Propranolol, Obsidan, Proprasylyt, Reducor, AY 64043, Dociton, ICI 45520, Inderal, 1-Isopropylamino-3-(1-naphthyloxy)-2-propanol, NSC-91523, Propanalol, Propanolol, Propranalol, Reducor line, etalong, Avlocardyl, Euprovasin, 525-66-6, NSC91523, 318-98-9, 1-(1-Naphthyloxy)-2-hydroxy-3-(isopropylamino)propane hydrochloride, 1-(Isopropylamino)-3-(.alpha.-naphthoxy)-2-propanol hydrochloride, 1-(Isopropylamino)-3-(1-naphthoxy)-propan-2-ol hydrochloride, 1-(Isopropylamino)-3-(1-naphthyloxy)propan-2-ol hydrochloride, 1-(Isopropylamino)-3-(1-napthyloxy)-2-propanol hydrochloride, 2-Propanol, 1- (isopropylamino)-3-(1-naphthyloxy)-, hydrochloride, 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride, AY 64043, Anaprilin, Anapriline, Avlocardyl, Berkolol, Beta Neg, Caridolol, Dociton, Herzbase, I 2065, ICI 45520, Ikopal, Inderal, Inderal hydrochloride, Inderalici, Inderex, Inderol, Kemi, Naprilin, Pranolol, Pronovan, Propanolol, Propranolol, Propranolol Hydrochloride, Propranolol chloride, Propranolon hydrochloride, (+-)-Propranolol, (1)-1-(Isopropylamino)-3-(naphthyloxy)propan-2-ol, 13013-17-7, 2-Propanol, 1-((1-methylethyl)amino)-3-(1-naphthalenyloxy)-, 2-Propanol, 1-((1-methylethyl)amino)-3-(1-naphthalenyloxy)-, (+-)- (9CI), 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, (+-)-, D,L-Propranolol, EINECS 235-867-6, Racemic propranolol, 1-(1-Naphthyloxy)-2-hydroxy-3-(isopropylamino)propane hydrochloride, 1-(Isopropylamino)-3-(.alpha.-naphthoxy)-2-propanol hydrochloride, 1-(Isopropylamino)-3-(1-naphthoxy)-propan-2-ol hydrochloride, 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol, 1-(Isopropylamino)-3-(1-naphthyloxy)propan-2-ol hydrochloride, 1-(Isopropylamino)-3-(1-napthyloxy)-2-propanol hydrochloride, 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-, hydrochloride, 2-Propanol, {1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-,} hydrochloride, 318-98-9, AIDS-159975, AIDS159975, AY 64043, Anaprilin, Anapriline, Avlocardyl, Berkolol, Beta Neg, Caridolol, Dociton, Herzbase, ICI 45520, Ikopal, Inderal, Inderal hydrochloride, Inderalici, Inderex, Inderol, Kemi, NSC91523, Naprilin, Pranolol, Pronovan,

Propanolol, **Propranolol**, **Propranolol Hydrochloride**, **Propranolol chloride**, **Propranolon hydrochloride**

Search for: **Propanolol**

Structure not available

IUPAC Name	1-naphthalen-1-yloxy-3-propan-2-ylamino-propan-2-ol
CAS Number	525-66-6
Chemical Formula	$C_{16}H_{21}NO_2$

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We Want You to Know Abo

Inderal (Propanolol

An Informative Guide for Parents

What Is Inderal? Inderal is a medication that is used to lower blood pressure and help the heart beat normally.

How Does Inderal Work? The heart and the blood vessels are made of muscle. This medication relaxes the muscle of the heart and blood vessels. It may be given to your child for several reasons:

1. If your child has Tetralogy of Fallot this medicine will help relax the heart muscle so that blood can get into the lung artery.

2. If your child has an irregular heart beat it will help prevent the irregular beats from happening.

3. If your child has high blood pressure it will help to keep the blood pressure normal by relaxing the blood vessels and the heart muscle.

When It Works

Inderal is given by mouth. It is absorbed from the stomach into the blood. The effect of the medication wears off after 6 hours and that is why it is given four times a day. It is best to give it before each meal and at bedtime.

As your child gains weight, the amount of medicine may be increased. You must bring your child for regular doctor visits.

What Are The Safeguards?

Usually there are no problems. But, a problem could occur if there is too much Inderal in your child's body. This can be serious if not treated. We want to preve this or treat this when it happens. This is why it is very important to bring your child for regular doctor visits. It is also important to know when to call for help.

Inderal (Propanolol)

When Might Problems Occur?

Problems may happen most often after:

□ Child first starts Inderal

□ Amount is increased

□ Other medicines your child is taking are changed

□ Child becomes ill - especially with vomiting or diarrhea

Precautions When Using This Medicine

1. Your child may have nausea, vomiting, stomach cramps, and diarrhea or constipation when taking this medicine. To help prevent these problems, this medicine should be taken with a full glass of water, juice or milk.

2. Other problems that may happen when taking this medicine are: confusion, light-headedness, breathing problems, sleeping problems, cold hands and fee

If any of the above problems happen contact your doctor. He/She may change th amount of medicine your child is receiving.

When To Call For Help

About the Medication:

1. If you have trouble giving your child the Inderal.
2. If your child has repeated vomiting or diarrhea.
3. If your child has a cold or flu with vomiting or diarrhea.
4. If 2 or more doses of Inderal are missed in a row.
5. If 1 dose of Inderal has been missed for 2 or more days.
6. If your child does not eat, drink, or urinate like (s)he usually does.

Other Signs And Symptoms To Call About

You need to call your doctor immediately if any of the following takes place.

1. If your child has any difficulty in breathing such as shortness of breath or wheezing.

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2. If he/she has any swelling.
3. If your child faints.
4. If he/she has a slow or irregular heart beat or chest pain. Your doctor may ask you to check the child's heart-beat daily while on this medication, and will te you how fast it should be. If the heart beat is slower than it should be, the doctor may tell you not to give the drug that day.

How To Give The Medicine

1. The label on the bottle will tell you how much medicine to give your child. Read the label carefully every time you give the medicine.

2. Wash and dry your hands before handing the medicine.

3. Stay with your child until he/she has taken the medicine.

4. If the medicine is a pill then give it with a glass of water, milk or fruit juice. If the medicine is a liquid then shake the bottle well before drawing it up into a syringe. Check to see if it is the exact dose. Make sure you are measuring onl the medicine and not any air bubbles trapped in the medicine.

5. Hold the dropper at eye level to be sure it is the exact dose.

6. Make sure your child's head is elevated to prevent choking.

7. Slowly drop the medicine onto the child's tongue or side of the mouth. Make sure the child swallows the medication. Rinse the dropper in water and dry before putting it back in the medicine bottle. This will keep germs from growing in the medicine.

8. Store Inderal out of the reach of children.

It Is Important To Remember

1. Give exact amount of Inderal that is ordered. Do not stop giving this medicine or change the amount given without first talking with your cardiologist. Usua the doctor will give your child less medication over several days or weeks before stopping it completely.

2. If too much is accidentally taken, immediately call the Poison Control Center of your state and call your doctor (Florida's Poison Control Center: 1-800-282-3171).

3. Mix Inderal with only small amounts of foods or fluids if this is the only way

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the child will take it.

4. If you miss a dose you can give it as soon as possible. If it is almost time for

the next dose, skip the missed dose and go back to your regular schedule. Do not try to make up for it by doubling or increasing the next dose. give the exa amount when the next dose is given.

5. Give Inderal at the times ordered. For example: 1-2 hours before or after the ordered time is not going to create problems, but try not to change the schedu beyond that. If your child is awake one hour before the medicine is due or if your child sleeps until one hour after the medicine is due, it is okay to give it them at this time.

6. If your child vomits after you give the medicine, ***do not give it again***. Wait until the next dose is due.

7. Be sure to get the prescription refilled before the last dose is given. When you doctor decides the medicine is no longer needed, get rid of this medication properly.

Suggestions

Mark off on your daily calendar when you give the medication to help you get in the habit of this daily routine. Try to give the medication at the same time every day.

Every family should have a 1 ounce bottle of Syrup of Ipecac in their home to be used in case of poisoning. Use it only after you call the Poison Control Center. Sometimes, causing a child to vomit can make the child's condition worse.

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Agent Name	**Propanolol**
Alternative Name	Inderal
CAS Number	525-66-6
Formula	C16-H21-N-O2
Major Category	Other Chemicals
Synonyms	Betalong; 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)-; 2-Propanol, 1-((1-methylethyl)amino)-3-(1-naphthalenyloxy)-; beta-Propranolol; Proprasylyt; Reducor; [ChemIDplus]
Category	Pharmaceuticals
Sources/Uses	Used as an antihypertensive drug;
Comments	Allergic contact dermatitis reported in pharmaceutical workers; [Kanerva, p. 1182]
Reference Link	Occupational contact dermatitis from propranolol
Adverse Effects	
Skin Sensitizer	Yes
Links to Other NLM Databases	
Health Studies	Human Health Effects from Hazardous Substances Data Bank: PROPRANOLOL HYDROCHLORIDE
Toxicity Information	Search TOXNET
Chemical Information	Search ChemIDplus
Related Information in Haz-Map	
Diseases	Diseases associated with exposure to this agent: • Contact dermatitis, allergic

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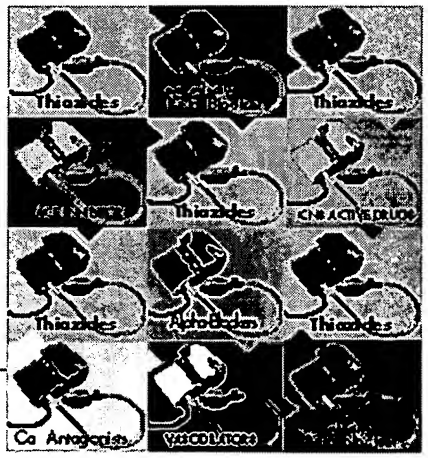
Therapeutics Letter, issue 8, July/August 1995



Drugs of Choice in the Treatment of Hypertension

(Part 2)

After review of the long term hypertension studies, including the epidemiologic and randomized placebo controlled drug trials, certain clinically important facts stand out:

- Risk of cardiovascular events correlates better with systolic than diastolic blood pressure.(1)
- Risk correlates better with blood pressures taken outside the doctor's office than with office blood pressures.(2)
- Blood pressure consistently decreases with placebo treatment (10/8 mm Hg).(3)
- The average additional blood pressure fall in the active treatment group is modest (11/6 mm Hg).(3), (4)
- The average blood pressure fall with treatment in trials using low doses of just one drug (7-9.5/46.5mm Hg) (5), (6) is similar to that obtained from an overview of trials using high doses of multiple drugs (11/6 mm Hg).(3), (4)

These facts suggest the following ways to assist in managing your patients with hypertension:

- Put more emphasis on systolic and home blood pressures when making treatment decisions.
- Appreciate that some of the blood pressure lowering effect seen in the office is due to the placebo effect. In **other** words, no matter what you are prescribing, it is likely to appear efficacious.

- Realize that *pushing* the dose seldom improves the antihypertensive effect. Likewise, the dose can frequently be lowered in patients receiving high doses of antihypertensive drugs without changing the antihypertensive effect.

In Part 1 we summarized the published evidence demonstrating that if we want to be certain of reducing morbidity and mortality in our hypertensive patients, a low-dose thiazide diuretic is the best choice. However, we obviously need the use of more than one class of antihypertensive drugs. Beyond the thiazides, we have much less evidence of effectiveness in decreasing cardiovascular events. **We cannot assume that drugs which are equivalent in lowering blood pressure will prove to be equally effective in reducing morbidity and mortality.**

What is the evidence that beta blockers decrease morbidity and mortality in hypertensive patients?

There are only two trials in which the effectiveness of beta blockers (propranolol(3) and atenolol(7)) can be compared with placebo. When the data from these trials are combined, there is a trend towards a reduction in the incidence of total stroke, log odds ratio, 0.77 (0.59-1.04), but little effect on total coronary events, 0.89 (0.71-1.13). The lack of effectiveness of atenolol based therapy in reducing coronary events corroborates that seen in **other** studies. (8), (9) It may be that the high cardioselectivity of atenolol is not a desirable pharmacological action.

There are three trials(3), (7), (10) in which the effectiveness of beta blockers can be compared with thiazides. When the results of these trials are combined in a meta-analysis the patients receiving thiazide had a non statistically significant reduction in the incidence of stroke, 0.81 (0.58-1.14)and coronary events, 0.92 (0.74-1.14). In post myocardial infarction trials, non-selective beta blockers and high dose beta-1 selective blockers, but not oxprenolol or pindolol, beta blockers with high partial agonist (increased sympathomimetic) activity, reduce risk of reinfarction and mortality. (11) **With the evidence presently available, it is advisable when prescribing beta blockers to use a non-selective beta blocker in the lowest dose required to lower the blood pressure** (see Table).

In what hypertensive patient is a beta blocker the drug of first choice?

To lower blood pressure in patients with angina pectoris a beta blocker is the drug of first choice. Although we do not have the evidence, it also seems reasonable to use a beta blocker as first choice in patients where the drug can be used to treat more than the hypertension, eg. patients with frequent recurrent migraine or patients with sympathetic hyperactivity, resting tachycardia, and palpitations. Beta blockers should not be used in patients with asthma or **other** forms of obstructive airways disease.

Table 1: Beta Blockers

Beta Blockers	Trade Name	Usual Dosage Range	Daily Cost *(x)*
Propanolol*	**Inderal®, generic** **Inderal® LA**	**20-120 mg BID** **60-240 mg daily**	**$0.08-$0.24** **$0.47-$1.66**
Nadolol*	**Corgard®, generic**	**20-160 mg daily**	**$0.15-$0.79**
Timolol*	**Blocadren®, generic**	**5-20 mg BID**	**$0.36-$1.05**
Atenolol°	Tenormin®, generic	25-100 mg daily	$0.20-$0.66
Metoprolol°	Betaloc®, Lopressor®, generic Betaloc® SR, Lopressor® SR	25-100 mg BID 100-200 mg daily	$0.26-$0.48 $0.41-$0.71
Acebutolol^	Sectral®, Monitan®, generic	100-400 mg daily	$0.44-$1.32
Oxprenolol^	Trasicor® Slow Trasicor®	20-160 mg BID 80-320 mg daily	$0.31-$1.65 $0.83-$1.66
Pindolol*^	Visken®, generic	5-15 mg BID	$0.52-$1.31
Labetalol*[a]	Trandate®	100-400 mg BID	$0.52-$1.82

* non-selective || ° selective || ^ partial agonist || ª alpha blocker

(x) Average or lowest cost alternative (LCA) price in BC, 1994.

In what hypertensive patient is an ACE inhibitor the drug of first choice?

ACE inhibitors have been clearly shown to prolong survival in patients with congestive heart failure.(12) They are therefore the obvious first choice in patients with hypertension and CHF. It is not established at the present time whether ACE inhibitors have a unique renal protective effect in diabetic nephropathy.(13)

A recent study suggests that ACE inhibitors increase the risk of hypoglycemia in treated diabetic patients.(14) There are no proven therapeutic differences between the ACE inhibitors; drug choice can be made based on convenience and cost. (see Table). The cost can be minimized by prescribing 1/4 or 1/2 tablets whenever possible. (e.g.1/4 of a 20 or 40 mg tablet of quinapril costs $0.23 a day).

Table 2: ACE Inhibitors

ACE Inhibitors	Trade Name	Usual Dosage Range	Daily Cost *(x)*
Quinapril	**Accupril®**	**5-40 mg daily**	**$0.92 all tablets**
Ramipril	**Altace®**	**1.25-10 mg daily**	**$0.72-$1.01**
Captopril	**Capoten®, generic**	**12.5-50 mg daily**	**$0.45-$1.19**
Perindopril	Coversyl®	2-8 mg daily	$0.68-$1.28
Benazepril	Lotensin®	5-40 mg daily	$0.61-$1.64
Cilazapril	Inhibace®	1-10 mg daily	$0.65-$1.69
Lisinopril	Prinivil®, Zestril	5-40 mg daily	$0.70-$2.10
Fosinopril	Monopril®	10-40 mg daily	$0.84-$2.01
Enalapril	Vasotec®	5-40 mg daily	$0.82-$2.36

(x) Average or lowest cost alternative (LCA) price in BC, 1994.

In what hypertensive patient is a calcium antagonist the drug of first choice?

At the present time there are no outcome studies which identify a group of patients who would specifically benefit from a calcium antagonist. It is clear that post MI patients with left ventricular dysfunction do worse with diltiazem than with placebo.(15) An overview of 31 placebo controlled trials submitted to the United States Food and Drug Administration (16) reported that patients receiving calcium antagonists had a 63% excess of cardiac events, as compared to placebo.

A recent unpublished but highly publicized study also suggests that patients receiving a calcium antagonist for hypertension have a significantly increased risk of myocardial infarction compared with patients receiving diuretics or beta blockers. Neither of these studies are definitive. They do, however, reinforce the message in this and the previous letter, and emphasize the need for prospective randomized controlled studies measuring morbidity and mortality. These trials are under way, but we cannot expect any results for 4 - 5 years.

Table 3: Calcium Antagonists

Calcium Antagonists	Trade Name	Usual Dosage Range	Daily Cost *(x)*
Diltiazem	Cardizem®, generic	60-120 mg BID, TID	$0.77-$2.32
	Cardizem SR®	60-180 mg BID	$1.50-$3.60
	Cardizem CD®	120-300 mg daily	$1.35-$2.98
	Isoptin®, generic	80-160 mg BID, TID	$0.62-$1.85

Verapamil	Isoptin SR®	120-240 mg BID	$2.07-$3.08
	Verelan®	120-480 mg daily	$0.88-$2.45
Nifedipine	Adalat®, generic	5-30 mg BID, TID	$0.55-$1.27
	Adalat PA®	10-30 mg BID	$0.99-$2.54
	Adalat XL®	30-90 mg daily	$1.00-$2.56
Felodipine	Plendil®, Renedil®	2.5-20 mg daily	$0.54-$2.12
Amlodipine	Norvasc®	5-10 mg daily	$1.33-$1.94
Nicardipine	Cardene®	20-40 mg TID	$1.85-$3.70

(x) Average or lowest cost alternative (LCA) price in BC, 1994.

In what hypertensive patients are second drugs useful?

From the large controlled studies of the treatment of mild hypertension it is clear that in at least 50% of patients the BP can be controlled with a thiazide alone. The additional drugs used in these studies, for patients not controlled with a thiazide include reserpine in three studies, methyldopa in two studies, hydralazine in two studies, and beta blockers in two studies. We thus can have some confidence in the effectiveness of these drugs used in combination with a thiazide. In patients with moderate to severe hypertension 3 to 4 drugs are often required to adequately control the blood pressure. We, therefore, are fortunate to have a wide armamentarium of drugs to choose from (see Tables).

Conclusion

It is up to the clinician, through systematic therapeutic trials, to identify the drug(s) which are efficacious, well tolerated in low doses, convenient, and affordable to the patient and society. **We should use the drugs proven to reduce morbidity and mortality as much as possible, but occasionally we are forced to individualize and choose based on other factors.**

Table 4: Alpha 1 Blockers

Alpha 1 Blockers	Trade Name	Usual Dosage range	Daily Cost *(x)*
Prazosin	Minipress®, generic	1-10 mg BID	$0.34-$1.32
Terazosin	Hytrin®	1-20 mg daily	$0.64-$2.94
Doxazosin	Cardura®	1-16 mg daily	$0.58-$3.60

(x) Average or lowest cost alternative (LCA) price in BC, 1994.

Table 5: Central and Peripheral Sympatholytics

Central and Peripheral Sympatholytics	Trade Name	Usual Dosage Range	Daily Cost *(x)*
Reserpine	Serpasil®, generic	0.0625-0.25 mg daily	<<$0.01
Methyldopa	Aldomet®, generic	125 mg - 1 g daily	$0.08-$0.50
Clonidine	Catapres®, generic	0.05-0.3 mg BID	$0.20-$1.06

(x) Average or lowest cost alternative (LCA) price in BC, 1994.

Table 6: Direct Vasodilators

Direct Vasodilators	Trade Name	Usual Dosage Range	Daily Cost *(x)*
Hydralazine	Apresoline®, generic	25-100 mg BID	$0.35-$1.08

Minoxidil	Loniten®	2.5-40 mg daily	$0.34-$2.96

* Average or lowest cost alternative (LCA) price in BC, 1994.

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1: Toxicol Appl Pharmacol. 1996 Mar;137(1):1-7. Related Articles, Links

ELSEVIER FULLTEXT ARTICLE

The effects of extracellular ions on beta-blocker cardiotoxicity.

Kerns W 2nd, Ransom M, Tomaszewski C, Kline J, Raymond R.

Department of Emergency Medicine, Division of Toxicology, Carolinas Medical Center, Charlotte, North Carolina 28232-2861, USA.

The mechanism of beta-blocker induced cardiotoxicity is poorly understood. One possible explanation is that beta-blockers induce ion dyshomeostasis, resulting in cardiac hyperpolarization. The intent of this study was to determine if modifying extracellular ions would reverse cardiotoxicity from two beta-blockers: propranolol (PROP) and atenolol (ATEN). Two treatments were studied: low extracellular K+ and high extracellular Na+. Isolated rat hearts were perfused on a Langendorff apparatus with Krebs-Henseleit-Bicarbonate buffer (KHB) solution. Toxicity (Tox) was induced by perfusing hearts for 30 min with KHB + PROP [5 microgram/ml] or KHB + ATEN [2.5 mg/ml]. Subsequently, hearts were perfused with KHB containing either PROP or ATEN, but modified by lowering K+ [2.3 mM] or raising Na+ [160 mM] for a 30-min treatment (Tx) period. Hearts were paced near the end of treatment. Cardiodynamics were monitored via a balloon-tipped catheter in the left ventricle. The first derivative of LV pressure (dP/dt) with respect to time served as our index of myocardial performance. Tx groups were as follows: (1) KHB only, (2) PROP only, (3) PROP + K, (4) PROP + Na, (5) ATEN only, (6) ATEN 4 K, and (7) ATEN + Na. PROP induced negative chronotropic effects and rendered the hearts refractory to pacing. ATEN demonstrated similar chronotropic toxicity plus decreased myocardial contractility. Tx with low extracellular K+ and high extracellular Na+ increased HR and restored the ability to pace, thereby reversing toxicity. These data suggest that beta-blocker toxicity is mediated via hyperpolarization.

PMID: 8607134 [PubMed - indexed for MEDLINE]

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1: J Pharmacol Exp Ther. 1978 Jan;204(1):226-9. Related Articles, Links

Blockade of tissue uptake of the antineoplastic agent, doxorubicin.

Somberg J, Cagin N, Levitt B, Bounous H, Ready P, Leonard D, Anagnostopoulos C.

Myocardial uptake of doxorubicin (Adriamycin) and its inhibition by digoxin and propranolol were studied in paced, isolated perfused cat hearts using tritiated doxorubicin. Contractility was studied using a Walton-Brody strain gauge arch and its first derivative. Coronary blood flow was measured by collecting the effluent from the heart. The myocardial content of doxorubicin was 0.069 +/- 0.101 nmol/mg after 30 minutes. Combined administration of doxorubicin and digoxin reduced the myocardial content of doxorubicin to 0.025 +/- 0.010 nmol/mg (P less than .02). The combination increased contractility compared with doxorubicin alone and increased coronary blood flow compared with digoxin alone. The reduction in the myocardial content of digoxin by doxorubicin was not significant. Propranolol also reduced the myocardial uptake of doxorubicin (P less than .05) without changing coronary blood flow and without further reducing contractility. Thus, both propranolol and digoxin merit evaluation in preventing doxorubicin cardiotoxicity.

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Abstract

Alcoholism: Clinical and Experimental Research
Volume 25 Page 882 - June 2001
doi:10.1111/j.1530-0277.2001.tb02294.x

Volume 25 Issue 6

Cardioprotective Effect of Propranolol From Alcohol-Induced Heart Muscle Damage as Assessed by Plasma Cardiac Troponin-T

Vinood B. Patel[1], Raheela Ajmal[1], Roy A. Sherwood[1], Andrew Sullivan[1], Peter J. Richardson[1], and Victor R. Preedy[1]

Background: Heavy alcohol consumption from either long-term misuse or binge drinking is associated with poor cardiac contractility, mitochondrial dysfunction, and ventricular arrhythmias. The aim of this study was to measure circulating cardiac troponin-T as a marker for myocardial damage following acute and chronic alcohol administration.

Methods: In acute studies, male Wistar rats were treated with alcohol (75 mmol/kg body weight, intraperitoneal) and plasma was collected 2.5 hr after alcohol administration for analysis of rat cardiac troponin-T. In addition, rats were pretreated with cyanamide (an inhibitor of acetaldehyde dehydrogenase), various beta-blockers, xanthine oxidase inhibitors, or lisinopril before acute alcohol dosing. In chronic studies, rats were fed alcohol (as 35% of total dietary calories) for 6 weeks.

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Affiliations

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- **Results:** The results of the time course study showed that acute alcohol administration significantly raised plasma cardiac troponin-T levels after 2.5 hr and 6 hr, but not after 24 hr. The effects of alcohol on cardiac troponin-T were potentiated with cyanamide pretreatment. Acute ethanol, alone or with cyanamide pretreatment, decreased systolic blood pressure and increased heart rates. Beta-blocker pretreatment with propranolol reduced the alcohol-induced increase in plasma troponin-T, whereas lisinopril potentiated this effect. The beta-blockers, atenolol and metoprolol, and the xanthine oxidase inhibitors, allopurinol and oxypurinol, were unable to reduce elevated troponin-T. However, pretreatment with the beta-blocker timolol moderated the acute alcohol-induced increase in troponin-T. In the chronic alcohol rat model, no differences were observed between alcohol and control pair-fed rats, suggesting the inducement of tolerance.

Conclusions: In conditions of acute exposure, ethanol-induced lesions are characterized by raised plasma cardiac troponin-T possibly due to β_1 and/or β_2 adrenergic activation.

References PDF [107KB]

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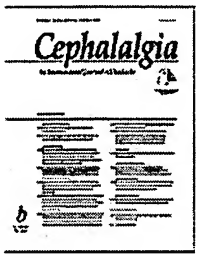

Abstract

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Side Effects - Symptoms & Solutions

Cardiotoxicity and Cardiomyopathy

What are cardiotoxicity and cardiomyopathy?

Cardiotoxicity is a condition when there is damage to the heart muscle. As a result of **cardiotoxicity**, your heart may not be able to pump blood through out your body as well. This may be due to chemotherapy drugs, or other medications you may be taking to control your disease. **Cardiotoxicity**,
if severe, may lead to cardiomyopathy.

Cardiomyopathy - Is often a result of treatments, such as chemotherapeutic medications, or may be caused by a group of diseases or disorders, that lead to damaged heart muscle. Injury to heart muscle may cause a disturbance in the heart's pumping action, and subsequent heart failure.

Cardiomyopathy may be result of:

- Viruses - such as human immunodeficiency virus (HIV)
- Amyloidosis - a malignant disease where a stretchy, thick (amyloid) protein, may deposit on your heart or other organs, and cause cardiomyopathy
- Infection
- Long-standing high blood pressure
- Chronic or long-term alcohol use
- Diabetes
- Thyroid disease, such as hyperthyroidism
- Thiamine and Vitamin B deficiency
- Medications, such as certain types of chemotherapy may lead to cardiomyopathy. Medications that may commonly cause **cardiotoxicity**, or cardiomyopathy, are called anthracyclines. Anthracyclines may be used to treat leukemia, lymphoma, multiple myeloma, breast cancer, and sarcoma. These drugs may also be used in other cancers, if your healthcare provider thinks it is necessary. A commonly used anthracycline is called doxorubicin (Adriamycin®).
- Cardiomyopathy may also result from genetic defects

- With certain drugs, such as doxorubicin, there is a dose at which these cardiotoxic effects on the heart may occur. Your doctor or healthcare provider will follow you closely if you are receiving these drugs.
- Before you receive a chemotherapy drug that may cause **cardiotoxicity**, your healthcare provider may order an echocardiogram, or a radionuclide ventriculography scan, to determine how well your heart is functioning at its' baseline. The tests will most likely be repeated during and after your chemotherapy treatments, as your doctor or healthcare provider recommends. This is how they will monitor your heart function while receiving cardiotoxic medications.
- The ejection fraction (EF) is a percentage of blood pumped out into the body during each heartbeat. An EF of 50%-75% is considered normal. The lower the ejection fraction, the more severe the heart failure may be. This may determine if the cardiotoxic drug has caused cardiomyopathy.

You may have developed cardiomyopathy if your doctor finds:

- An enlarged heart muscle on chest x-ray (caused by the heart working harder to pump blood through the body
- Abnormal heart or lung sounds on physical examination
- Swelling in your hands, feet, or unusual weight gain

What are some symptoms to look for?

- You may be overly tired, or very weak (fatigued). It may be hard for you to do any kind of your normal activities.
- You may have "coughing spells", or a long-term (chronic) cough, if your **cardiotoxicity** results in heart failure (such as congestive heart failure).
- You may experience shortness of breath, either at rest or while performing any type of activity. This may include walking to the door, or climbing stairs.
- You may have trouble lying flat in bed, and you may have to sleep on 2 or more pillows. Your shortness of breath may cause you to wake up in the middle of the night.
- Your legs may be swollen, especially in your feet and ankles.
- You may gain water weight easily, or feel bloated.

Things you can do:

- Make sure you tell your doctor, as well as all healthcare providers, about any other medications you are taking (including over-the-counter, vitamins, or herbal remedies).
- Remind your doctor or healthcare provider if you have a history of diabetes, liver, kidney, or heart disease.
- If you are experiencing severe cardiomyopathy, which may have caused heart failure, you may be told to reduce the amount of salt you are eating in a day. Many times, it may be restricted to about 2 grams of sodium per day. A diet lower in salt may decrease the amount of work that is placed on your heart. You should discuss this with your healthcare provider how you can specifically use your diet to control your symptoms of heart failure.
- Try to exercise, as tolerated, to maintain your optimal level of functioning. Discuss with your healthcare provider how you can create a specific exercise program to suit

your needs. Make sure to exercise, under the supervision of your healthcare provider. Walking, swimming, or light aerobic activity may help you to lose weight, and promote the flow of oxygen in your lungs and blood. It may also help to strengthen your heart muscle.

- If your heart damage is due to amyloidosis, you should be seeing an oncologist and a cardiologist who work together, to coordinate your care.
- If your heart damage is due to infection, diabetes, thyroid disorders, or long-standing high blood pressure, it is important to discuss with your healthcare provider how you may treat the disease, and optimize your level of functioning.
- With severe cardiomyopathy, sleeping at night with your head of the bed elevated may make it easier to breathe. You may do this by sleeping on extra pillows.
- Use relaxation techniques to decrease the amount of anxiety you have. If you feel anxious, place yourself in a quiet environment, and close your eyes. Take slow, steady, deep breaths, and try to concentrate on things that have relaxed you in the past (such as a vacation, an area of your home, etc.).
- You should restrict the amount of alcohol you take in, or avoid it all together. Alcohol may adversely interact with many medications.
- If you are ordered a medication to treat this disorder, do not stop taking any medication unless your healthcare provider tells you to. Take the medication exactly as directed. Do not share your pills with anyone.
- If you miss a dose of your medication, discuss with your healthcare provider what you should do.
- If you experience symptoms or side effects, especially if severe, be sure to discuss them with your health care team. They can prescribe medications and/or offer other suggestions that are effective in managing such problems.
- Keep all your appointments for your treatments.

Drugs that may be prescribed by your doctor:

Your doctor or healthcare provider may prescribe certain drugs to help your heart muscle work more effectively. Depending on the extent of **cardiotoxicity** you have experienced, and your overall health status, your doctor may recommend reducing the dose of the medication that caused the heart damage, stopping the medication, or changing to a different regimen. Some of the common drugs that are used to treat **cardiotoxicity** may include:

- **Dexrazoxane hydrochloride** - May be used to prevent or reduce the occurrence and severity of heart damage (cardiomyopathy) caused by doxorubicin (Adriamycin®).
- **ACE inhibitors** - These drugs work by opening, or dilating, your arteries. They will lower your blood pressure, and improve blood flow to your kidneys, and through out your body. Your healthcare provider may also prescribe these medications if you have diabetes or protein in your urine, to protect your kidneys. Some examples of this medication may include: enalapril maleate (Vasotec®), lisinopril (Zestril®), and fosinopril sodium (Monopril®)
- **Beta-blockers** - can be used to slow down your heart rate, and improve blood flow through your body. You may take this drug if you have been diagnosed with irregular heartbeats, palpitations, heart failure, or high blood pressure. Some examples of this

medication may include: metoprolol (Lopressor®), propranolol (Inderal®), and atenolol (Tenormin®).

- **Diuretics** - may be known as "water pills", as they work to prevent or treat heart failure by making you urinate out extra fluid. Some examples of this medication may include furosemide (Lasix®), and hydrochlorthiazide. You may receive this medication alone or in combination with other medications.
- **Digoxin** - Also called digitalis, this medication works by slowing down the heart rate, and making it beat more effectively. This will pump blood through out the body better. It is also called Lanoxin®.
- **Vasodilators** -are drugs that work by opening up or "dilating" the vessels. These may include isosorbide dinitrate (Isordil®).
- Do not stop any of these medications abruptly, as serious side effects may occur

When to call your doctor or health care provider:

- Fever of 100.5° F (38° C), chills, sore throat (possible signs of infection).
- Shortness of breath, chest pain or discomfort; swelling of your lips or throat should be evaluated immediately
- Feeling your heart beat rapidly (palpitations)
- Any new rashes on your skin
- Any unusual swelling in your feet and legs
- Weight gain of greater than 3 to 5 pounds in 1 week.

Note: We strongly encourage you to talk with your health care professional about your specific medical condition and treatments. The information contained in this website is meant to be helpful and educational, but is not a substitute for medical advice.

Cardiotoxicity

From Wikipedia, the free encyclopedia
(Redirected from Cardiotoxic)

Cardiotoxicity is the occurrence of heart muscle damage. The heart becomes weaker and isn't as efficient in pumping and therefore circulating blood. **Cardiotoxicity** may be caused by chemotherapy treatment.

See also

- Heart failure

References

- Chemocare.com: [1] (http://www.chemocare.com/managing/fullstory.sps?iNewsid=24392)

Retrieved from "http://en.wikipedia.org/wiki/**Cardiotoxicity**"

Categories: Cardiology

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Alcoholism Official Journal of the Research Society on Alcoholism
CLINICAL AND EXPERIMENTAL RESEARCH

ARTICLE LINKS:
Fulltext | PDF (106 K)

Cardioprotective Effect of Propranolol From Alcohol-Induced Heart Muscle Damage as Assessed by Plasma Cardiac Troponin-T.

Alcohol Effects on the Fetus, Brain, Liver, and Other Organ Systems

Alcoholism: Clinical & Experimental Research. 25(6):882-889, June 2001.
Patel, Vinood B.; Ajmal, Raheela; Sherwood, Roy A.; Sullivan, Andrew; Richardson, Peter J.; Preedy, Victor R.

Abstract:
Background: Heavy alcohol consumption from either long-term misuse or binge drinking is associated with poor cardiac contractility, mitochondrial dysfunction, and ventricular arrhythmias. The aim of this study was to measure circulating cardiac troponin-T as a marker for myocardial damage following acute and chronic alcohol administration.

Methods: In acute studies, male Wistar rats were treated with alcohol (75 mmol/kg body weight, intraperitoneal) and plasma was collected 2.5 hr after alcohol administration for analysis of rat cardiac troponin-T. In addition, rats were pretreated with cyanamide (an inhibitor of acetaldehyde dehydrogenase), various beta-blockers, xanthine oxidase inhibitors, or lisinopril before acute alcohol dosing. In chronic studies, rats were fed alcohol (as 35% of total dietary calories) for 6 weeks.

Results: The results of the time course study showed that acute alcohol administration significantly raised plasma cardiac troponin-T levels after 2.5 hr and 6 hr, but not after 24 hr. The effects of alcohol on cardiac troponin-T were potentiated with cyanamide pretreatment. Acute ethanol, alone or with cyanamide pretreatment, decreased systolic blood pressure and increased heart rates. Beta-blocker pretreatment with propranolol reduced the alcohol-induced increase in plasma troponin-T, whereas lisinopril potentiated this effect. The beta-blockers, atenolol and metoprolol, and the xanthine oxidase inhibitors, allopurinol and oxypurinol, were unable to reduce elevated troponin-T. However, pretreatment with the beta-blocker timolol moderated the acute alcohol-induced increase in troponin-T. In the chronic alcohol rat model, no differences were observed between alcohol and control pair-fed rats, suggesting the inducement of tolerance.

Conclusions: In conditions of acute exposure, ethanol-induced lesions are characterized by raised plasma cardiac troponin-T possibly due to [beta]1 and/or [beta]2 adrenergic activation.

Note: Performing your original search, ***propranolol adriamycin***, in PubMed will retrieve ***39*** citations.

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1: Cardiovasc Res. 1983 Jan;17(1):43-9. Related Articles, Links

Verapamil, propranolol, and hydralazine protect against the acute cardiac depression induced by adriamycin.

Wikman-Coffelt J, Rapcsak M, Sievers R, Rouleau JL, Parmley WW.

The apex ejecting isolated rat heart perfused with media containing 3 X 10(-5) mol . litre-1 adriamycin for 40 min demonstrated the following changes in contraction patterns: (a) a ten-fold increase in end-diastolic pressure; (b) a 45% decrease in developed pressure; (c) a 17% decrease in coronary flow; (d) a 27% increase in time to peak pressure; (e) a 26% increase in time for pressure to fall 50% during relaxation; and (f) a 65% decrease in maximum (+) and (-) dP/dt. In rats pretreated 1 h before death, verapamil, propranolol, and hydralazine significantly attenuated the cardiac depression produced by adriamycin. The combinations of verapamil and hydralazine, or propranolol and hydralazine were especially efficacious. Particularly striking was the protection afforded against an increase in diastolic pressure. Digoxin pretreatment afforded no protection. It is postulated that the acute depressive effects of adriamycin may be related to calcium overload.

PMID: 6850716 [PubMed - indexed for MEDLINE]

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Note: Performing your original search, ***propranolol adriamycin***, in PubMed will retrieve ***39*** citations.

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1: Res Commun Chem Pathol Pharmacol. 1978 Sep;21(3):577-80. Related Articles, Links

Potentiation of the toxicity of adriamycin by propranolol.

Choe JY, Combs AB, Folkers K.

Both propranolol and adriamycin are biochemically known to inhibit mitochondrial CoQ10-enzymes of myocardial tissue in vitro. Both propranolol and adriamycin are clinically known to cause cardiotoxicity. At two dose levels of propranolol which caused no deaths to mice when administered alone, significant potentiation (p less than 0.01) of the lethality of adriamycin to mice was observed. These data, projected to the clinical situation, seem to contraindicate the administration of the beta-blocker, propranolol, for the hypertension of a cancer patient who is being treated with adriamycin.

PMID: 705032 [PubMed - indexed for MEDLINE]

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